

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

GROUP: 1791

Benjamin CHU, et al.

SERIAL NO: 10/674,464

EXAMINER: TENTONI, LEO

FILED: October 1, 2003

FOR: ELECTRO-BLOWING TECHNOLOGY FOR FABRICATION OF FIBROUS
ARTICLES AND ITS APPLICATIONS OF HYALURONAN

DECLARATION UNDER 37 C.F.R. § 1.131

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes Benjamin Chu, Benjamin S. Hsaio, Dufei Fang and Akio Okamoto who
depose and state that:

1. We are the inventors of the invention in the present application.
2. The Examiner has rejected the claims of the present patent application in light of the combination of Published US Application 2005/0067732 to Kim et al (hereafter the "Kim" reference) and Published US Application 2004/0146546 to Gravett et al (hereafter the "Gravett" reference). In order to demonstrate that we were in possession of our invention prior to the effective dates of either of the Kim or Gravett references, we provide the following information.
3. The present invention was made in the United States or in a NAFTA or WTO member country.
4. It is our understanding that the earliest effective prior art date of the Kim reference is November 20, 2002.
5. It is our understanding that the earliest effective prior art date of the Gravett reference is September 26, 2002.
6. In August, 2002, inventors Chu, Hsiao, and Fang submitted a research proposal to the U.S. Army Small Business Innovation Research (SBIR) Program. Attached as Exhibit A is

a copy of the proposal description submitted along with the Proposal Cover Sheet, dated August 14, 2002.

7. The research proposal was submitted naming three of the current co-inventors (Chu, Hsiao and Fang) as principal investigators, while Okamoto was not named on the research proposal. The omission of Okamoto from the research proposal was due to the fact that Okamoto was not part of the same University as Chu, Hsiao and Fang, but was rather an employee of a private company from Japan. Thus, Okamoto's name was not included in the research proposal submitted by the University and Drs. Chu, Hsiao and Fang.

8. The research proposal submitted to the SBIR Program describes our invention sufficiently to show that we had conceived the invention of combining electrospinning and melt blowing into a single process for formation of hyaluronan (hyaluronic acid) polymer fibers prior to the effective November 20, 2002 date of the Kim reference and prior to the effective September 26, 2002 date of the Gravett reference.

9. In particular, attention is drawn to Section 3.3 beginning at page 6 of the proposal, which describes the aspect of the proposed research which combines electrospinning and melt blowing to gain the combined effects of electrostatic repulsions and the high velocity of the gas stream on the fibers begin generated.

10. Additional attention is drawn to page 2 of the research proposal, which mentions several patent applications filed by certain of the inventors prior to submission of the research proposal. Copies of the patents (US 6,685,956; US 6,689,374; US 7,172,765; and 6,713,011) resulting from the applications mentioned in the research proposal are attached as Exhibit B. While none of these patents describes the electroblowing process of the present invention, the inclusion of hyaluronan polymer in these patents and the discussion of these patents in the research proposal clearly shows that hyaluronan polymer was one of the polymers conceived of for the present invention (see, e.g., column 4, lines 25-29 of US

6,685,956; column 4, lines 29-33 of US 6,689,374; column 4, lines 27-32 of US 7,172,765; and column 13, lines 40-46 of US 6,713,011).

11. Attached also as Exhibit C is the letter from the Army dated November 11, 2002, notifying us that our proposal had been selected for negotiation and possible contract award.

12. We conceived our invention prior to the effective dates of each of the Kim and Gravett references, as evidenced by our research proposal to the Army SBIR Program. Accordingly, neither the Kim reference nor the Gravett reference is available as prior art against the present application.

13. We diligently worked on reducing the invention to practice over the months after approval of the research proposal, culminating in the filing of the present patent application on October 1, 2003.

14. The undersigned declarants declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

15. Further deponents saith not.

Ben Chu

Signature: Benjamin Chu

Date

9/4/2009

Ben Hsiao

Signature: Benjamin S. Hsiao

9-4-09

Date

Dufei Fang

Signature: Dufei Fang

9-8-09

Date

Signature: Akio Okamoto

Date

Customer Number

22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 05/06)

15. Further deponents saith not.

Signature: Benjamin Chu

Date

Signature: Benjamin S. Hsiao

Date

Signature: Dufei Fang

Date

Signature: Akio Okamoto

Date September 5, 2009

Customer Number

22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 05/06)

EXHIBIT A

Small Business Innovation Research (SBIR) Program
Proposal Cover Sheet

Proposal Number: A022-2903 Agency: Army DUNS: 101394430
Topic Number: A02-193 CAGE:
Proposal Title: Novel Clothing Nonwoven Liner Material - Nanofibers in Melt Blown Media

Firm:

Firm Name: Stonybrook Technology and Applied Research, Inc.
Mail Address: P.O. Box 1336

Stony Brook, New York 11790

Website Address:

Proposed Cost: 69889 Phase: I Duration: 6
Option Cost: 49975 Option Duration: 4

Business Certification: (Check all that apply)

Are you a small business as described in paragraph 2.2 ? YES
Number of employees including all affiliates (average for preceding 12 months): 3
Are you a socially or economically disadvantaged business as defined in paragraph 2.3 ? NO
Are you a woman-owned small business as described in paragraph 2.4 ? NO
Has this proposal been submitted to other US government agencies, or DoD components or other SBIR activity? NO
If yes, list the name(s) of the agency, DoD component or other SBIR office and Topic Number in the space below.

Project Manager/Principal Investigator

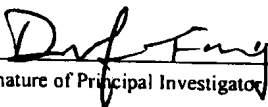
Name: Dr. Dufei Fang
Title: Director of Technology
Phone: (631) 838-7796
Fax: (631) 632-6518
E-Mail: dfangstar@aol.com

Corporate Official (Business)

Name: Dr. Ben Chu
Title: President
Phone: (631) 632-7928
Fax: (631) 632-6518
E-Mail: bchu@notes.cc.sunysb.edu

For any purpose other than to evaluate the proposal, this data except proposal cover sheets shall not be disclosed outside the Government and shall not be duplicated, used or disclosed in whole or in part, provided that if a contract is awarded to this proposer as a result of or in connection with the submission of this data, the Government shall have the right to duplicate, use or disclose the data to the extent provided in the funding agreement. This restriction does not limit the Government's right to use information contained in the data if it is obtained from another source without restriction. The data subject to this restriction is contained on the pages of the proposal listed on the line below.

Proprietary Information:


Signature of Principal Investigator

8/14/02
Date

Signature of Corporate Business Official

Date

Technical Abstract (Limit your abstract to 200 words with no classified or proprietary information)

This Small Business Innovation Research Phase I Project aims to develop innovative key technology to combine the melt-blown process with Multi-Jet electrospinning process that can fabricate membranes with new microfiber/nanofiber hybrid morphology and can lead to a commercial scale-up process. The specific aims of this Phase I proposal are to implement several new designs to incorporate the Multi-Jet electrospinning process (patent pending) in the conventional melt-blown process. Complex and coupled processing parameters including novel spinneret assemblies, new electrode designs, and control of jet acceleration, transportation and manipulation will be considered. The unique Multi-Jet electrospinning has been developed by the PI from Stonybrook Technology and Applied Research (STAR), Inc. and scientists from the Chemistry Department in the State University of New York at Stony Brook (SUNYSB). This technology is capable of producing new nanostructured membranes with hybrid nanofiber/nanoparticle morphology, designed composition variations and 3D pattern formation.

Anticipated Benefits/Potential Commercial Applications of the Research or Development. (No classified or proprietary information)
Non-woven protective clothing with functions of non-wetting and low absorption could be used in many situations. Thus it will have high potentials for commercialization

List a maximum of 8 Key Words that describe the Project.

multi-jet Electrospinning, nanofiber, non-woven, melt-blown, co-spinning

**Small Business Innovation Research (SBIR) Program
Cost Proposal**

Firm: Stonybrook Technology and Applied Research, Inc.
Address: P.O. Box 1336
Stony Brook, NY 11790

Location Where Work Will Be Performed: Rm. 416, Chemistry Bldg., SUNY/SB, Stony Brook, NY 11794-3400

Proposal #: A022-2903

Title of Proposed Effort: Novel Clothing Nonwoven Liner Material - Nanofibers in Melt Blown Media

Firm's Taxpayer ID: 11-3503753

CAGE Code:

DUNS: 101394430

Topic Number: A02-193

Topic Title: Novel Clothing Nonwoven Liner Material - Nanofibers in Melt Blown Media

TOTAL DOLLAR AMOUNT FOR THIS PROPOSAL:

\$119,864.40

DIRECT LABOR:

	Phase I:			Option:		
Category and/or Individual:	Rate/Hour	Est.Hours	Cost	Rate/Hour	Est.Hours	Cost
Dufei Fang	31.25	200	6,250.00	31.25	250	7,812.50
Post-Doc Researcher	16.50	1040	17,160.00	16.50	680	11,220.00
Subtotal Direct Labor (DL):			23,410.00			19,032.50
Fringe Benefits, if not included in Overhead, (rate 30.6000 %) x DL =			7,163.46			5,823.95
Labor Overhead (rate 15.0000 %) x (DL + Fringe) =			4,586.02			3,728.47
Total Direct Labor (TDL):			35,159.48			28,584.92

DIRECT MATERIAL COSTS:

	Phase I:	Option:
Melt-blown Assembly	20,000.00	7,500.00
Multiple-jet Electrospinning Assembly*	8,000.00	2,800.00
Lab supplies & testing materials	2,200.00	2,000.00
Subtotal Direct Materials Costs (DM):	30,200.00	12,300.00
Material Overhead (rate 15.0000 %) x DM:	4,530.00	1,845.00
Total Direct Materials Costs (TDM):	34,730.00	14,145.00

OTHER DIRECT COSTS:

	Phase I:	Option:
Lab rental, utilities	0.00	4,300.00
Shop services	0.00	2,000.00
Subtotal Other Direct Costs (ODC):	0.00	6,300.00
Direct Cost Overhead (rate 15.0000 %) x ODC	0.00	945.00
Total Other Direct Costs (TODC):	0.00	7,245.00

G&A (rate 0.0000 %) x (base: TDL)

0.00

0.00

Total Cost:

69,889.48

49,974.92

Fee or Profit (rate 0.0000 %)

0.00

0.00

TOTAL ESTIMATED COST:

69,889.48

49,974.92

Explanatory material relating to the cost proposal:

1. We have to build a new melt-blown assembly, estimated initial investment is about \$25,000. We request \$20,000 and another \$7,500 in the optional period. 2. The cost of multiple jet is much higher than we requested. STAR is going to subsidise the investment for the assmebly. 3. Testing materials include polymers, solvent etc.

The cost breakdown portion must be signed by a responsible official.

Sign: Dufei Fang Date: 8/14/02

Name: Dufei Fang Title: Director of Technology

>>Has any executive agency of the United States Government performed any review of your accounts or records in connection with any other government prime contract or subcontract within the past twelve months? No

>>Will you require the use of any government property in the performance of this proposal? No

>>Specify the type of payment desired: Partial payments

1. Problems and Opportunities in Electrospinning Technology

1.1 Current State and Problem in Nano- and Micro-Fibers

Electrospinning is an atomization process of conducting fluid. It takes advantages of the interactions between the electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a charged semi-dilute polymer solution or a charged polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the jet stream can be collected as an interconnected web of fine sub-micron size fibers. The resulting films from these nanoscale fibers (nanofibers) have very large surface area to volume ratios and very small pore sizes.

The electrospinning technique was first developed by Zeleny [1] and patented by Formhals [2]. Up to now, there are about 50 patents on electrospinning technology. Much research has been done on how the jet is formed as a function of electrostatic field strength, fluid viscosity, and molecular weight of polymers in solution. In particular, the work of Taylor and others on electrically driven jets has laid the groundwork for electrospinning [3]. Although potential applications of this technology have been widely mentioned, which include biological membranes (substrates for immobilized enzymes and catalysts systems), wound dressing materials, artificial blood vessels, aerosol filters, clothing membranes for protection against environmental elements and battlefield threats [4-26], *no practical industrial process for electrospinning of polymer systems for fabric applications has ever been implemented*. The existing commercial electrospinning process by Donaldson, Inc. is limited for the manufacture of filter membranes, not of clothing. The major technical barrier for manufacturing electrospun fabrics for clothing is the speed of fabrication. In other words, as the fiber size becomes very small, the yield of the electrospinning process becomes very low. For example, if we consider a polymer melt being spun from the spinneret with a diameter of 700 μm and the final filament is formed with a diameter of 250 nm, the draw ratio will then be about 3×10^6 . As the typical throughput of the extrudate from a single spinneret is about 16 mg/min (or 1 g/hr), the final filament speed will be about 136 m/s, which is comparable to the highest speed (10,000 m/min or 167 m/s) attainable by the high-speed melt-spinning process. Thus, the throughput of the spinneret in electrospinning is about 1000 times lower than that in the commercial high-speed melt-spinning process.

1.2 Unique *e-Jets*TM Technology by STAR, Inc.

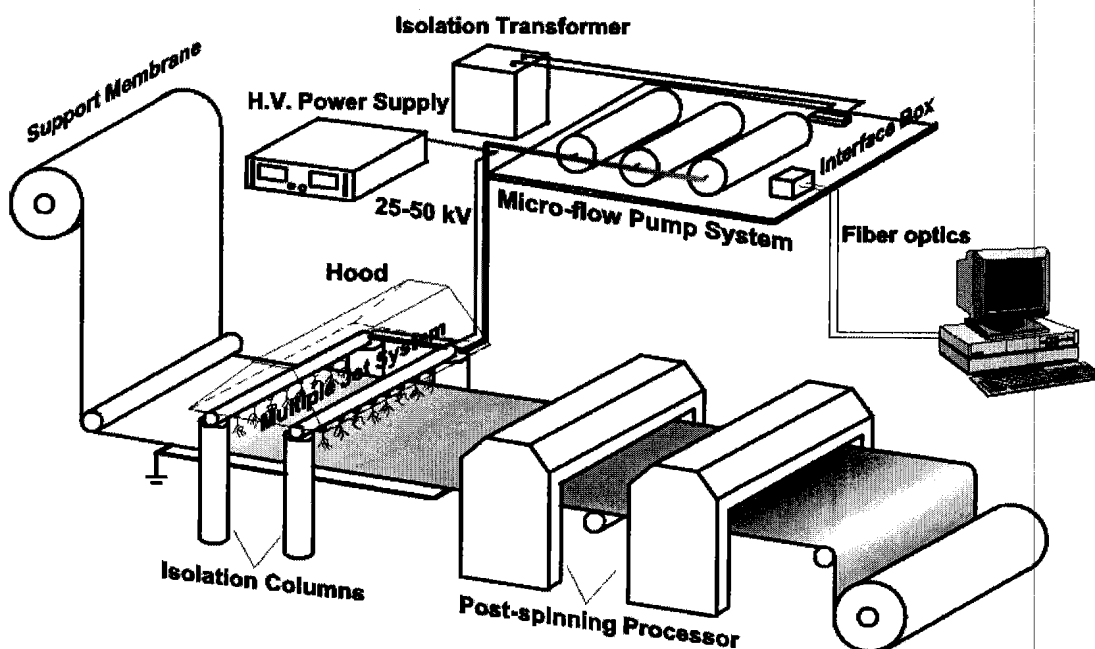
Another major technical problem for mass production of electrospun fabrics is the assembly of spinnerets during electrospinning. A straightforward multi-jet arrangement as in high-speed melt-spinning cannot be used because adjacent electrical fields often interfere with one another, making the mass production scheme by this approach very impractical.

A unique *e-Jets*TM technology for multiple-jet electrospinning process has recently been developed for manufacturing of non-woven membranes having fibers with diameters in the tens

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

of nanometer size range by the PI from Stonybrook Technology and Applied Research (STAR), Inc. and scientists from the Chemistry Department in the State University of New York at Stony Brook (SUNYSB). Three patent applications based upon this technology have been filed in 2001 by the PI and Co-PIs through SUNYSB (1. "Control and Manipulation of Electrospinning Process"; 2. "Bioabsorbable Membrane for Prevention of Post-Operative Adhesions", 3. "Novel Bioabsorbable Scaffolds for Cell Delivery Applications"). The Technology Transfer Center at SUNYSB has agreed to grant exclusive licensing of these patents to STAR, Inc., when approved. A schematic diagram of the prototype multi-jet electrospinning production unit (with one-dimensional array electrodes), based on the *e-Jets™* technology and tailored for making nanostructured bioabsorbable membranes for biomedical applications, is shown in Figure 1. The unique features of this apparatus can be summarized as follows.

Fig.1 Bioabsorbable Nanostructured Membrane Processing Unit



1. Innovation in the *e-Jets™* technology:
 - Finite element analysis on electric field distribution of multiple spinnerets.
 - New spinneret/electrode designs for multiple-jet operation.
 - Electric field control on jet streams (formation and acceleration)
 - 3D pattern design.
2. Combination of materials and processing development permits us to develop new membrane materials including:
 - Variations in porosity, pore size, and pore size distribution
 - Variation in nanofiber/nanoparticle morphology
 - Variation in degree of hydrophobicity
 - Construction of unique hierarchical structures (nano-, micro-, meso-).

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

We feel that, with some suitable modifications, the *e-Jets™* technology can be readily incorporated into the more conventional melt-blown process for manufacturing of new non-woven textile structures for fabrics, which forms the basis of this proposal.

1.3 Conventional Melt-Blown Process

The melt-blown process is a unique non-woven technology using high-velocity air to produce fibrous non-woven articles directly from polymer melts. This process is unique because it can be used to produce fibers with a large range of diameter (from 0.1 μm to 10 μm). The basic technology was first demonstrated by the Naval Research Laboratory in 1950s and was incorporated into the commercial process by Exxon Chemicals (now ExxonMobil) in 1970s. Recently, there have been some renewal interests to develop new microfiber materials by 3M, Eastman Kodak, Kimberly-Clark, and Fleetguard Filter.

The typical melt-blown process consists of the several elements: extruder, metering pumps, die assembly, web formation, and winding. The die assembly is the most critical element, which has three distinct parts: polymer-feed distribution, die nosepiece, and air manifolds. The feed distribution is usually designed in such a way that the polymer distribution is less dependent on the shear properties of the polymer, allowing for the process of widely different polymeric materials. The die nosepiece is a tapered and hollow piece of metal having several hundred spinnerets across the width. The extruded polymer melt filaments are subsequently attenuated by hot air to form fine fibers. (The web uniformity depends largely on the design of the nosepiece.) The high velocity hot air (primary air) is supplied by the air manifolds through the slots on the top and bottom sides of the die nosepiece. Typical air temperature ranges from 200°C to 350°C at velocity ranges from 0.5 to 0.7 times of the speed of sound. As the primary air stream containing the microfibers progresses toward the collector screen, it draws in a large amount of surrounding air (secondary air) that cools and solidifies the fibers. The fibers are generally laid randomly on the moving collector (usually a vacuum is applied to the inside). The collector speed and the collector distance from the die nosepiece can be varied to produce a variety of non-woven morphology.

2. Phase I Technical Objectives

This SBIR Phase I Project aims to develop a new form of technology that will combine the melt-blown process with the *e-Jets™* (multiple-jet electrospinning) technology. The key technology should permit fabrication of membranes with composite microfiber/nanofiber hybrid morphology and can lead to the production of nanostructured composite materials in new formats.

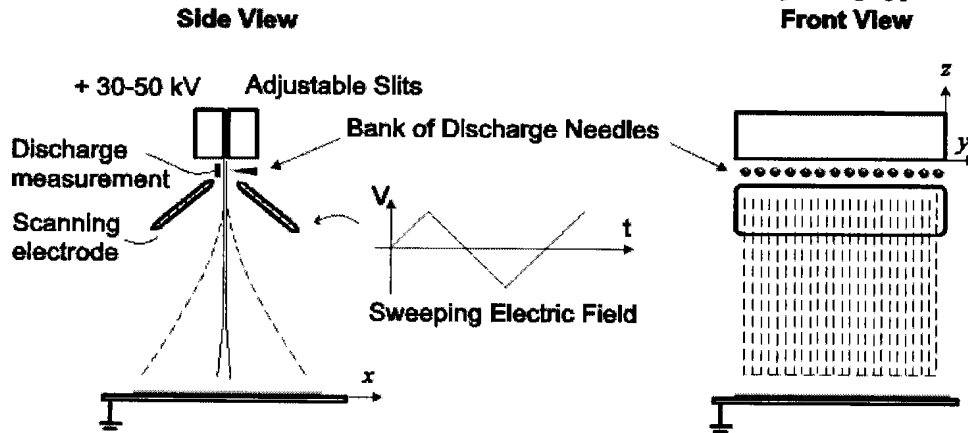
The specific aims of this Phase I proposal are to implement new designs in electrospinning/electrospraying technology in order to incorporate the *e-Jet™* technology (patent pending) with the more conventional melt-blown process. Complex and coupled processing parameters including novel spinneret assemblies, new electrode designs, and control of jet acceleration, transportation and manipulation will be considered.

3. Phase I Work Plan

3.1 Design 1 – Linear Electrical Field Enhanced Melt Spinning Assembly

Based on our unique *e-Jets*TM technology for electrospinning of polymer solutions, we propose to develop a prototype multi-jet apparatus for electrospinning of polymer melts. The conceptual design of a linear electrical field enhanced melt spinning assembly is shown in Figure 2, where a relatively high throughput of polymer melt (about 1 gm/min/spinneret) can be extruded from a pair of adjustable slits. The slit exit surfaces will contain microchannels with defined dimensions and separation distances. The presence of microchannels will provide the exit for fiber spinning. The slits are connected to the high voltage. The shape and separation distance of the spinning “holes” will be designed using a finite element analysis to simulate multi-jet electrospinning process, which will be described later. Under the electric field, the charged molecules in the melt will be stretched out and form bundles of repelling fibers in the flight path to the target plate. Different morphology in the membrane may be formed by tuning the spinning speed from the die. The amount of the electric charge in the polymer solution (excess charge) can be controlled by electric charge “spray”. In this case, a bank of discharge needles will be connected to another high voltage power supply and the charges in the corona zone of the needle tips will be transferred to the polymer melt. By utilizing this technique, 75% - 100% of excess charge may be obtained. A pair of steering (scanning) electrodes will be placed at the down stream but located very close to the bank of the discharge needles. By applying a sweeping voltage on to the scanning electrodes, a membrane with a controlled pattern formation can be obtained. The advantages of this proposed technique are: (1) relatively high throughput (high yield) – 1 to 2 orders of magnitude higher than the electrospinning of polymer solutions (2) no moving parts.

Figure 2. New slit-die design for the electric field enhanced melt-spinning apparatus



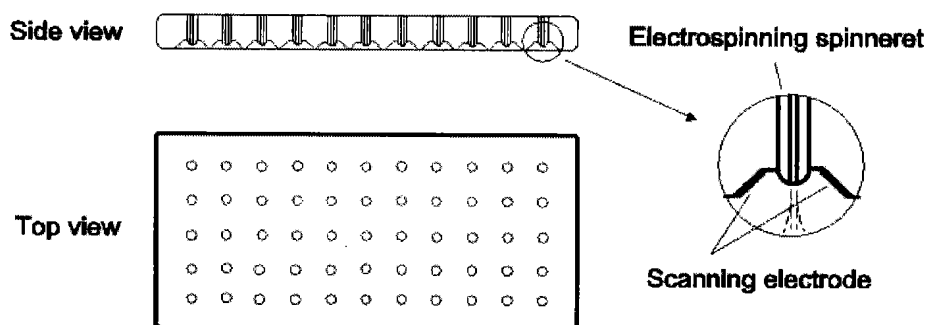
3.2 Design 2 – Two-Dimensional Multi-Jet Assembly

To explore the possibility to further increase the total electrospinning throughput, without the concerns of electrical field interference between the spinnerets, we propose to develop a prototype two-dimensional array of electrospinning spinnerets in an isolation matrix. This design is quite different from Design 1 where secondary electrodes were used to insulate the electrical field of each spinneret. The conceptual design of this apparatus is shown in Figure 3, where each spinneret has two pairs (X and Y direction) of miniature scanning electrodes. The

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

spinneret and the scanning electrodes are constructed in a way, based on the electrical field calculation, to minimize the interference between the adjacent electrodes. They are also electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret can be turned on/off independently by electricity (the response time thus should be relatively fast) a designed pattern can be obtained in the resultant membrane.

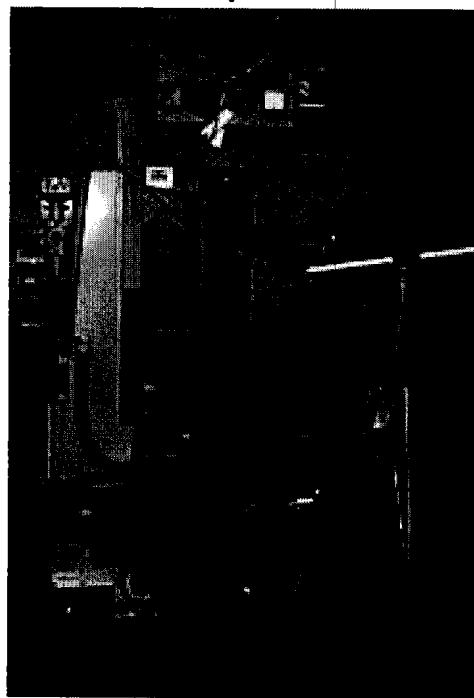
Figure 3 New designed array-spinneret pattern for electrospinning



Both Design 1 and Design 2 prototype multiple-jet electrospinning assemblies will be tested in a laboratory size portable melt spinning apparatus (photograph is shown in Figure 4). (This equipment was originally designed for on-line X-ray and Raman studies of melt-spinning process.) This apparatus consists of a 3/4" Independent Laboratory single screw extruder (C. W. Brabender Instr. Inc., NJ) and a custom-built vertical lifter with about 1.2 m of displacement (Applied Automation Research Corp., FL). The maximum extrusion temperature is about 325 °C. The extruder is mounted on a horizontal platform that can be translated in the vertical direction by computer control. The range of the typically used mass output rate of this extruder is 1-7 g/min.

The advantages of Design 1 (Linear Electrical Field Enhanced Melt Spinning Assembly) include the easy fabrication of the spinneret assembly, easy operation and maintenance, higher throughput rates. The disadvantages of this design include the difficulty in isolating the electric field distribution for each spinneret. In contrast, the advantages of Design 2 (Two-Dimensional Multi-Jet Assembly) include that the electric field of each spinneret will be isolated and that a more uniform fiber diameter and membrane morphology should be feasible. However, the disadvantages of this design are that the production and the operation of the spinning assembly may be more difficult. As both designs of the multi-jet assemblies will be tested, the one that provides the best

Figure 4. Portable extrusion apparatus at Stony Brook



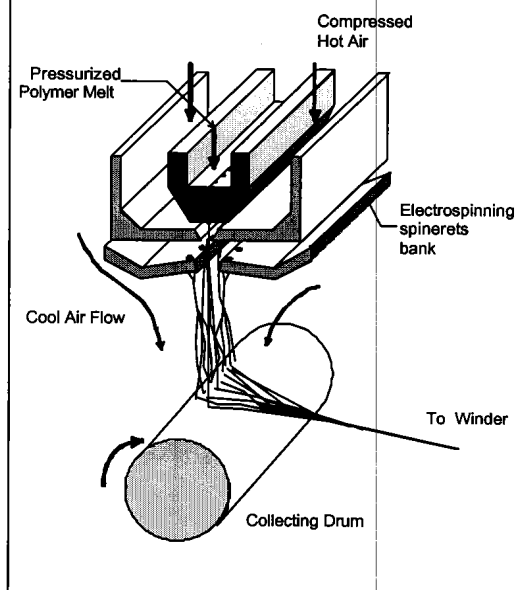
Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

performance will be incorporated with a laboratory scale melt-blown apparatus, whose scheme will be outlined next. Depending on the results from the experimental testing of both designs, we will also consider the possibility of a hybrid design by combining some unique features from each design.

3.3 Combination of Multi-Jet Electrospinning Technology and Melt-Blown Process

We propose to incorporate the best performing multi-jet electrospinning assembly in a laboratory melt-blown spinning apparatus using a slit-die or a pin-hole geometry. We term this *simultaneous co-spinning* design. The pin-hole assembly can be manufactured at SUNY-Stony Brook. The construction of the slit die assembly (polymer-feed distribution, die nosepiece, and air manifolds) for the melt-blown process can be contracted to the Hills, Inc. (West Melbourne, Florida), which is one of the leaders in the production of melt-blown manufacturing equipment. The feed distribution will be designed to minimize the shear properties of the polymer, allowing the melt blowing of widely different polymeric materials. We will probably choose the coat-hanger type feed distribution system because it gives both even polymer flow and even residence time across the full width of the die. The membrane uniformity depends largely on the design and fabrication of the nosepiece. Therefore, we will require very tight tolerances for the die nosepiece. There are two types of die nosepiece: capillary type and drilled holes type. We will probably choose the capillary type because the problems associated with precise drilling of very small holes can be avoided. In addition, the capillary tubes can be precisely aligned so that the holes follow a straight line accurately. The testing materials for the proposed study will be metallocene based isotactic polypropylene (iPP) of different molecular weights. This material is commonly used in melt-blown fabrics.

Figure 5 Schematic Diagram of Combined Multi-Jet Electrospinning and Melt-Blown Processes



A conceptual *simultaneous co-spinning* design to combine the multi-jet electrospinning technology and the melt-blown process is illustrated in Figure 5. In this design, the electrodes (electrospinning spinnerets) are aligned at a tilted angle with respect to the melt-spinning axis. The zone of instability of the jet will be immersed with the high velocity primary air, allowing the charged fibers to be extended and entangled with the melt-blown fibers. Additional air streams will also be applied in the down stream of the spin line to enhance the fiber mixing and to facilitate the fiber collection. The combined effects of electrostatic repulsions and the high velocity of the air stream will be utilized to create a new type of nanofiber morphology. In order to produce a 1-m width fabric, we plan to construct a large moving platform (ground electrode) for sample collection.

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

In this study, we have set a target ratio of 10% nanofibers (from electrospinning) and 90% microfibers (from melt-blown process) in the initial production of the non-woven fabric. We know that the surface area of this 10% nanofibers is about 10 times more than that of the 90% microfibers produced by the melt-blown process. Since the typical throughput from a single spinneret in electrospinning is about 1000 times smaller than that in the melt-blown spinning process, we plan to take the following steps to reach this goal. (1) The diameter of the melt-blown spinneret will be reduced and the air velocity will be reduced to the lowest value (such as 0.2 times of the speed of sound). This should reduce the throughput of the melt-blown spinning by more than 50 times. (2) A ratio of 10 spinnerets in electrospinning to 1 spinneret in melt-blown spinning will be implemented. This will increase the throughput of electrospinning by 10 times. These two steps should allow us to produce the fabrics with a nanofiber/microfiber ratio close to 10%. If necessary, we can further increase the content of the nanofibers by coating the simultaneously co-spun product using a sequential electrospinning method, as illustrated in Figure 1. We note that, the sequential electrospinning process can produce an asymmetric layered product.

3.4 Performance Evaluations of Hybrid Microfiber/Nanofiber Membranes

As requested by the Natick Soldier Center of this SBIR grant, we plan to demonstrate the co-spinning technology (melt blown and multi-jet electrospinning) that can be scaled up to manufacture a 1-meter width fabrics. Scientists from the Natick Soldier Center will test the following properties of the melt-blown/electrospun fabrics, under the guidance of or with the assistance. These properties will include (1) water vapor transport through the fabric, (2) air penetration through the fabric, (3) liquid (oil and water) retention within the fabric, and (4) liquid contact angle. The properties (air resistance, breath ability, water retention and liquid contact angle) will be optimized by fine-tuning the multiple operating parameters in the multi-jet electrospinning process. The routine characterizations of these membranes such as scanning electron microscopy (to study the membrane morphology), thermal analysis (to study the thermal properties such as melting and glass transition temperatures), mechanical properties, and X-ray scattering/diffraction (to study crystal structure and lamellar morphology) will also be carried out on an as-needed basis.

4. Related Work

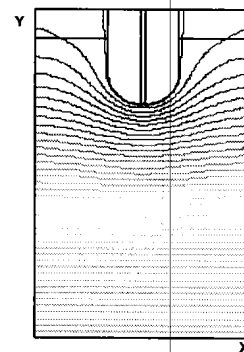
In the past three years, we have successfully developed a unique *e-Jets*TM technology (patent pending and *TM* being processed) at *STAR*, Inc. and at SUNY-Stony Brook. The key technology permits fabrication of membranes with composite nanofiber/nanoparticle hybrid morphology, designed composition variations, and 3D pattern formation from polymer solutions. This technology shall enable us to design a new multi-jet apparatus for melt-spinning that can also be incorporated in the melt-blown process to produce new microfiber/nanofiber composite non-woven fabrics. We will briefly outline the principle of the *e-Jets*TM technology and the innovation as follows.

4.1 Finite Element Analysis to Simulate Multi-Jet Electrospinning Processes

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

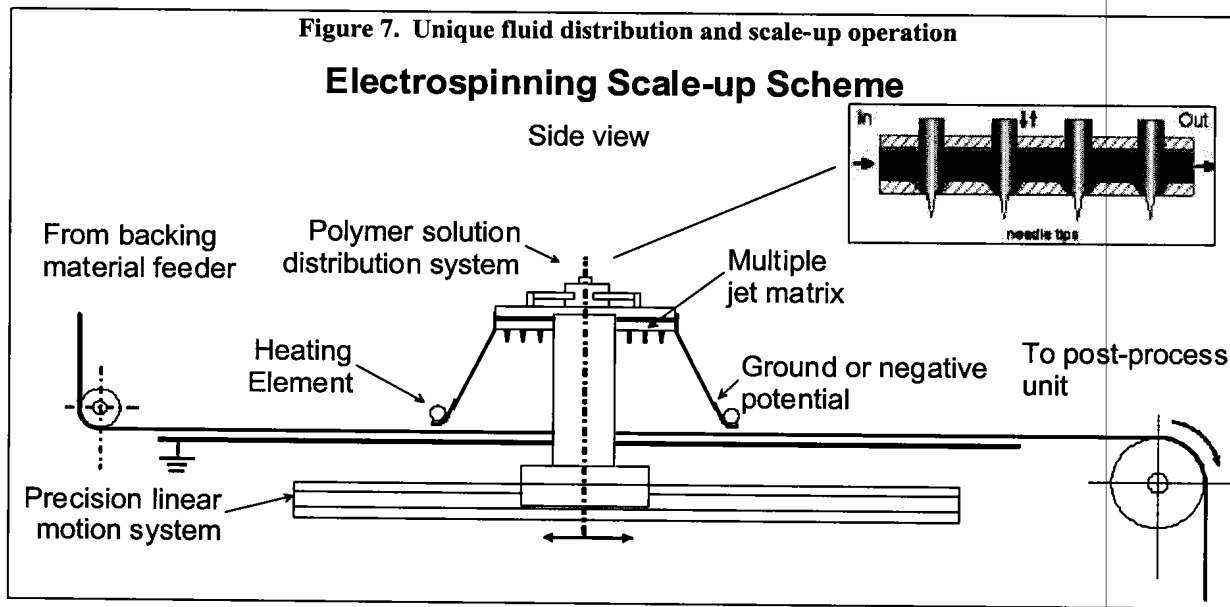
In the multi-jet electrospinning system, the electric field distribution is very complicated. The design of the multi-jet electrode array in the current apparatus was guided by the 2D finite element analysis (FEA) for electromagnetics using the software by Field Precision (www.fieldp.com). The software package included XLATE, MESH, ESTAT and VESTAT modules, which were used to numerically analyze the electric field distributions in complex electrode configurations. Extensive simulations for a single jet system involving parameters such as size, shape and potential of the electrode, distance between the electrode tip and the ground, the shape and materials surrounding the electrode were carried out (Figure 6). We have constructed several electrodes based on different designs and experimentally verified the electrode designs with the FEA simulations. The parameters obtained from simulations and experiments for the single jet were also used as basis for the design of the multi-jet system.

Figure 6, FEA simulation of a single jet



4.2 Polymer Fluid Distribution System for Multi-jet Electrospinning

Figure 7 shows a schematic diagram of the fluid distribution and the linear array electrode assembly of a prototype scale-up apparatus. The backing material for the membrane is fed into the system by a “convoy belt” method. The polymer solution is distributed to the multiple spinneret (up to 200) linear array system with minimum pressure drop (inset diagram). The array system is mounted on two electrically isolated posts that are seated on a pair of precision rails. This allows the array system to move along the “belt” direction back and forth. The precision rails can also be mounted on a “rocking” system so that the array can move in the direction perpendicular to the “belt” direction. The heating elements are implemented to control the solvent evaporation rate. The “belt” can be sent to another unit or a post- processing unit for manufacturing composite membranes.



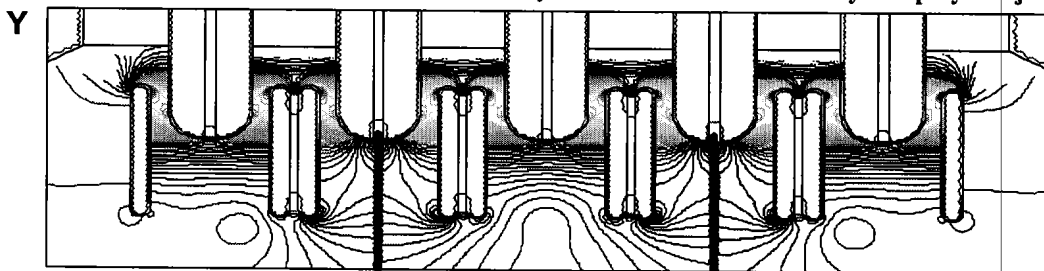
4.3 New Innovative Designs for The *e-Jets*TM Technology

Several new and innovative schemes to improve the control and manipulation of the electrospinning process have been implemented in order to control more precisely the fiber diameter and the membrane morphology. These methods are based on a combination of the principles of plasma physics and accelerator physics. They address two distinct processing issues in electrospinning: (1) the process for the jet formation and (2) the process for the jet acceleration. The principles of jet formation in an electrospinning process are similar to those of plasma formation in an “ion source”.

4.3.1 Use of Secondary and Tertiary Electrodes to Optimize Multi-jet Spinning

The use of secondary electrodes to shield each primary electrode (spinneret) has been implemented in our prototype apparatus. We note that the presence of secondary electrodes can weaken the field strength at the electrode tip. To overcome this problem, the geometrical shape, location and electric potential of the secondary electrodes has been optimized by the FEA simulations. We have optimized the designs with the parameters for single jet operation as a reference for multi-jet designs. The following two criteria have been met simultaneously in the design: (1) each electrode in the multi-jet system has the same electric field distributions, (2) the electric field strength on the electrode tip in the multi-jet system is the same as that in the single jet system. We have paid special attention to the field strength change before and after the jet formation. Figure 8 illustrates the simulation of electric field distribution for a 5-electrode system with two jets being formed. Results suggest that the interference of the neighboring electrodes (with and without the jet formation) of the optimized system is about 1% using the secondary electrodes. A real multi-jet system has been constructed based on the optimal parameters obtained from detailed FEA simulations. This analysis will also be carried out to optimize Design 1 and Design 2 of the multiple-jet electrodes assembly for melt spinning.

Figure 8. The FEA calculation of a 5-electrode system with formation of only two polymer jets.



We have also used a tertiary electrode to facilitate the membrane collection process during electrospinning. The tertiary electrode can be placed very close to the surface of the membrane. The electrode is connected to the ground with a negative potential in order to remove the surface charge accumulated by the electrospinning process efficiently.

4.3.2 Variation of Electrical/Mechanical Properties of Conducting Fluid

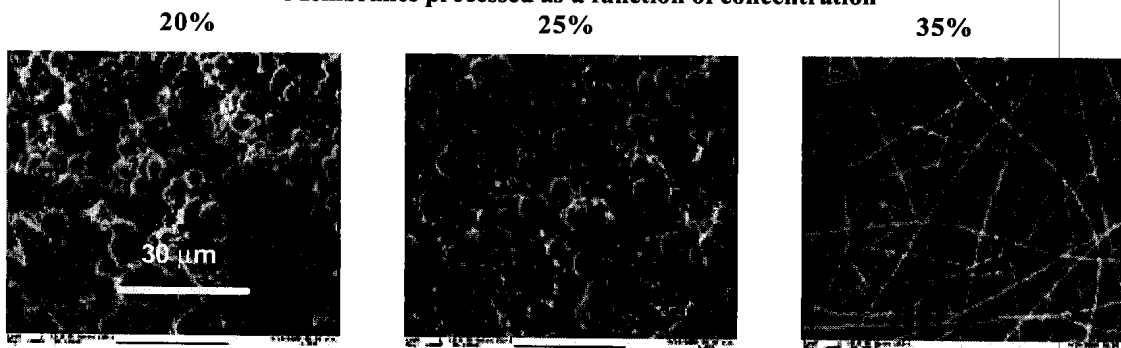
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The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magneto-hydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic field can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be alleviated.

The manipulation capability through processing parameters provides not only the means to control the fiber diameter, the membrane porosity but also the fiber/particle morphology of the membrane. The following process parameters have been explored for this purpose.

	Parameter	Methods
1. Fluid	Viscosity	Use of miscible solvents; polymer concentration
	Dielectric constant	Use of miscible solvents
	Surface tension	Addition of surfactants
	Viscoelastic property	Molecular weight/polydispersity and concentration
	Charge density	Change in ionic strength and pH; use of mixtures
	Polarizability	Use of miscible solvents
2. Fluid flow	Flow rate	Constant pressure or constant flow rate
3. Jet formation	Nozzle effect	Nozzle geometry
4. Jet acceleration	Electrostatic potential	Control of field strength and field geometry
	Electrostatic potential	Control of field strength and field geometry along the flight path, use of alternating gradients.

**Figure 9. SEM image of electrospun PLGA membranes with different morphology
Membranes processed as a function of concentration**



For example, we have investigated the effect of charge density (through the addition of salts) on the fiber diameter [27]. We found that the fiber diameter could be significantly changed by adding a small amount of salt in the solution. When 1 wt% potassium phosphate (KH_2PO_4) was added to the biodegradable poly(lactide-co-glycolide) PLA-co-PGA solution, the fiber diameter became much thinner than the one with no salt added. Thus, higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors

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the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4 , KIO_3 , and K_3PO_4), which are all biologically compatible to the body, will also be considered. We have demonstrated that the membrane morphology could be controlled by different processing parameters. By tuning the concentration, flow rate and/or solution viscosity, a membrane with different morphology (nanofiber to nanoparticle) could be obtained (Figure 9).

4.3.3 New Electrode Design and 2D Multi-jet Array Assembly for Solution Spinning

The designs of the electrospinning electrode have been intended to separate the jet formation process and the jet acceleration process using the following principle. The jet formation was treated as an “ion source”; the positively charged electrode was treated as the ‘anode’. The anode was responsible for the formation of the polymer solution droplet while the ‘cathode’ was a plate electrode with a small exit hole in the center. This exit hole provided the means to let the jet stream to pass through the cathode. If we take the polymer droplet on the anode to have a typical dimension of 2~3 mm and place the cathode at a distance of about 10 mm from the anode, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of the anode, the jet formation could be controlled and adjusted. Such an electrode configuration has greatly reduced the required applied potential on the anode from about 15 kilovolts (kV) down to typically 1.5 to 2 kV (relative to the cathode base potential). The anode potential required for a stable jet formation depends on the electric/mechanical properties of the conducting fluid.

Different from the linear array electrode assembly, a prototype two dimensional multi-jet system with 4x4 electrode/spinneret array assembly has been designed and constructed as shown in Figure 10. The polymer solution was introduced by a central inlet and then distributed to four quadrant sub-compartments. The electric potential V_0 was applied to the electrodes and another potential V_1 was applied to the secondary electrodes made by a metal plate. Experimental results showed that interference effects were low as expected. We are in the process of optimizing the parameters controlling the fluid flow and the electric field distributions for this system. Our target system in this proposal will be a 10x10 multi-jet system using the designs of primary, secondary and tertiary electrodes.

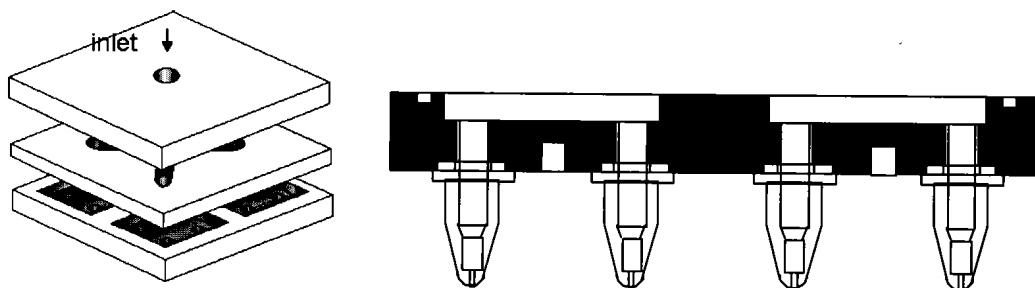


Figure 10. 3D view of the solution distribution system and the spinnerets mounting diagram.

4.3.4 Control of Jet Acceleration, Transportation and Manipulation

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The jet stream from the cathode exit hole is a stream that is positively charged. This stream has a tendency to straighten itself during flight. However, without the external electric field confinement, the jet will soon become unstable in its trajectory. In other words, the charged beam becomes defocused and thus the jet stream, with the intrinsic bending instability due to electrostatic repulsion of the charges within the jet stream, could not provide the desired function in controlling the microscopic and macroscopic properties of the fluid. This instability can be partially removed by using carefully designed probe electrodes immediately after the cathode plate and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the ion source at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the cathode base potential. The composite electrodes are capable to partially stabilize the jet stream.

The jet stream can also be focused by using an “Alternating Gradient” (AG) technique, widely used in the accelerator technology of high-energy physics. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The beam will be focused, for example, in the xz plane after the first lens and then be refocused in the yz plane after the second lens. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the ‘sweep’ potential, a desired pattern on the target can be formed by using this technology.

The combination of above four schemes (4.3.1-4.3.4) form the basis of the unique *e-Jets™* technology.

5. Research Milestones (6 months Phase I + 4 months Option Period) and Future Research and Development

The research milestones for the first 6 months of this Phase 1 project and the second 4 months of the Option Period are summarized below.

	<i>Month1-3</i>	<i>Month4-6</i>	<i>Month 7-8</i>	<i>Month 9-10</i>
<i>Design 1 Construction and Testing</i>	X			
<i>Design 2 Construction and Testing</i>	X			
<i>Combination of Melt-Blown Process with Multiple-Jet Electrospinning</i>		X		
<i>Membrane Property Evaluations (air resistance, breathability, water retention and liquid contact angle)</i>			X	X
<i>Optimization of Designs and Processing Variables</i>			X	X

The successful operation of this Phase I project will include (1) the demonstration of a multiple-jet electrospinning unit that can be scaled-up and incorporated in the conventional melt-

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blown process, (2) the fabrication of a new class of non-woven materials containing microfiber/nanofiber hybrid morphology, which possesses superior liquid and vapor transport properties. If successful, the technology base developed in Phase I will be fully extended to develop a commercially viable system with scale-up capability. At that point, a potential joint venture with ExxonMobil or other willing partner will be explored.

4. Commercialization Strategy

If successful, we plan to incorporate the best performing multi-jet electrospinning assembly in a commercial melt-blown spinning facility to evaluate the scale-up capability in the Phase II study. We will try to first secure the intellectual right at STAR, Inc. and then to explore a partnership relationship with a commercial outfit that is specialized in the melt-blown technology. One such company may be the Baytown Polymer Center, ExxonMobil Chemical Company. One of the Co-PIs (Ben Hsiao) is currently a consultant with ExxonMobil and has been conducting the research project on “Flow-Induced Crystallization in Polyolefins” with them since 1998. Currently, ExxonMobil is the leader in the melt-blown technology development, holding most of the licenses and/or options to produce microfiber non-woven and melt-blown equipment. We will also consider other companies such as 3M, Eastman Kodak, Kimberly-Clark, and Fleetguard Filter for potential partners.

5. Key Personnel (PI and Co-PIs)

Stonybrook Technology & Applied Research, Inc., (STAR) was established by three scientists (Benjamin Chu, Benjamin S. Hsiao and DuFei Fang) in 1999. They aim to take advantage of their complimentary knowledge in chemistry, materials science and engineering, and physics to (1) develop unique technologies and (2) produce specific cost-effective products, made of polymers and nano-composites. Their combined expertise includes chemical knowledge on polymer synthesis, physical processing methods, as well as advanced technology on molecular structure and macroscopic property relationships that permit predictions on a range of specific functional properties of materials. The initial emphasis of *STAR* will be on the development of electrospinning technology for applications to biomedical products dealing with anti-adhesion membranes, cell delivery and pain management. The qualifications and the responsibility of PI/Co-PIs for this proposal are summarized below.

DuFei Fang, Ph.D. (Principal Investigator) is the Technology Director of Stonybrook Technology and Applied Research, Inc. (STAR). He is an experimental physicist with background in accelerator physics and plasma physics. He has extensive experience in the instrumentation design and construction for free electron laser and synchrotron X-ray facilities. He has designed a prototype electrospinning apparatus with commercial scale-up possibility. DF was a professor and group leader at the Institute of Modern Physics, Fudan University (China) and also a visiting Fellow at Fitzwilliam College, Cambridge University (U.K.). He will be responsible for instrumentation implementation and optimization of the electrospinning process.

Ben Chu, Ph.D. (Co-PI) is a Distinguished Professor with joint appointment in both the Chemistry Department and the Department of Materials and Engineering at Stony Brook with specialization in hydrogels, polyelectrolyte, surfactant complexes, nanostructure modifications,

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ion-containing polymers, colloid science and DNA capillary electrophoresis. A High Polymer Physics Prize winner, BC is an executive member of the State University of New York (SUNY) Beam line at X3, a Co-Spokesperson for the Advanced Polymers Beam line (APB) at X27C of National Synchrotron Light Source (NSLS), and is serving as one of the Co-PIs in the ChemMat CARS at the Advanced Photon Source. He will be responsible for the studies of structure/property/process relationships of the electrospun membranes from polymer melts.

Ben Hsiao, Ph.D. (Co-PI), a Professor in the Chemistry Department at Stony Brook, came from the Fibers and CR&D Departments at DuPont and has extensive synchrotron experience and research expertise in the area of structure, morphology, property, functionality and processing relationships in biodegradable polymers, suture fibers and nanocomposites. BH is the Spokesperson for the APB at X27C of NSLS. He will be responsible for incorporation of the multiple-jet electrospinning prototype apparatus with the melt-blown process. BH is a long-time consultant with ExxonMobil and has several on-going research projects on fiber spinning with them.

6. Facility and Equipment

The STAR, Inc. occupies 600 square ft of space in the Chemistry Building at SUNY SB. Through the Chemistry Department, researchers can access scanning electron microscope (SEM), transmission electron microscope (TEM), scanning transmission X-ray microscope (STXM), Gamma-irradiation facilities, HRTEM and the synchrotron X-ray scattering beamlines (X3A2, X27C) in the National Synchrotron Light Sources (NSLS), Brookhaven National Laboratory. At Stony Brook, melt-spinning and solution spinning devices, atomic force microscope, (AFM) several high-resolution nucleus magnetic resonance (NMR) instruments (¹³C-, ¹H-), differential scanning calorimetry (DSC), Fourier Transform Infrared (FTIR), Raman Spectroscopy, tensile testing machines and rheometers are also available. Other capabilities include a rotating anode X-ray generator, forced Rayleigh scattering, centrifuge ball viscometry, magnetic needle rheometry, and DNA capillary electrophoresis. Machine shop is also available.

7. Literature Cited

1. Zeleny, J., Phys. Rev. 1914. 3: p.69-91.
2. Formhals, A., "Process and Apparatus for Preparing Artificial Threads", US Patent 1934: 1,975,504.
3. Taylor, G.I., Proc. Roy. Soc. Lond. A. 1969.31: p.453-475.
4. Deitzel, J. M.; Kosik, W.; McKnight, S. H.; Beck Tan, N. C.; DeSimone, J. M.; Crette, S., Electrospinning of polymer nanofibers with specific surface chemistry., Polymer 2001, 43(3): p.1025-1029.
5. Koombhongse, Sureeporn; Liu, Wenxia; Reneker, Darrell H., Flat polymer ribbons and other shapes by electrospinning., J. Polym. Sci., Part B: Polym. Phys., 2001, 39(21): p.2598-2606.
6. Shin, Y. M.; Hohman, M. M.; Brenner, M. P.; Rutledge, G. C., Experimental characterization of electrospinning: the electrically forced jet and instabilities., Polymer, 2001, 42(25): p.09955-09967.

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

7. Bognitzki, Mikhail; Frese, Thomas; Steinhart, Martin; Greiner, Andreas; Wendorff, Joachim H.; Schaper, Andreas; Hellwig, Michael. Preparation of fibers with nanoscaled morphologies: electrospinning of polymer blends. *Polym. Eng. Sci.*, 2001, 41(6): p.982-989.
8. Stitzel, Joel D.; Bowlin, Gary L.; Mansfield, Kevin; Wnek, Gary E.; Simpson, David G., Electrospinning and electrospinning of polymers for biomedical applications. Poly(lactic-co-glycolic acid) and poly(ethylene-co-vinylacetate)., International SAMPE Technical Conference, 2000, 32: p.205-211
9. Shin, Y. M.; Hohman, M. M.; Brenner, M. P.; Rutledge, G. C., Electrospinning: A whipping fluid jet generates submicron polymer fibers., *Appl. Phys. Lett.*, 2001, 78(8): p.1149-1151.
10. Bognitzki, Michael; Hou, Haoqing; Ishaque, Michael; Frese, Thomas; Hellwig, Michael; Schwarte, Christoph; Schaper, Andreas; Wendorff, Joachim H.; Greiner, Andreas, Polymer, metal, and hybrid nano- and mesotubes by coating degradable polymer template fibers (TUFT process). *Adv. Mater. (Weinheim, Ger.)*, 2000, 12(9): p.637-640.
11. Spivak, A. F.; Dzenis, Y. A., A condition of the existence of a conductive liquid meniscus in an external electric field. *J. Appl. Mech.*, 1999, 66(4): p.026-1028.
12. Fong, H.; Chun, I.; Reneker, D. H., Beaded nanofibers formed during electrospinning. *Polymer*, 1999, 40(16):p.4585-4592.
13. Reneker, Darrell H.; Chun, Iksoo., Nanometer diameter fibers of polymer, produced by electrospinning. *Nanotechnology*, 1996, 7(3): p.216-223.
14. Gibson, P., Schreuder-Gibson, H., and Pentheny, C., Electrospinning Technology: Direct Application of Tailorable Ultrathin Membranes. *J. Coated Fabrics*, 1998. 28: p. 63-72.
15. Fang, X., and Reneker, D.H., DNA Fibers by Electrospinning. *J. Macromol. Sci.-Phys.*, 1997. B36(2): p.169-173.
16. Doshi, J., and Reneker, D.H., Electrospinning Process and Applications of Electrospun Fibers. *J. Electrostatics*, 1995. 35: p.151-160.
17. Baumgarten, P.K., Electrostatic Spinning of Acrylic Microfibers. *J. Colloid Interface Sci.*, 1971. 36: p.71-79.
18. Larrondo, L., and St. John Manley, R., Electrostatic Fiber Spinning from Polymer Melts. I. Experimental Observations on Fiber Formation and Properties. *J. Polym. Sci.: Polym. Phys. Ed.*, 1981. 19: p.909-920
19. Larrondo, L., and St. John Manley, R., Electrostatic Fiber Spinning from Polymer Melts. II. Examination of the Flow Field in an Electrically Driven Jet. *J. Polym. Sci.: Polym. Phys. Ed.*, 1981. 19: p.921-932
20. Larrondo, L., and St. John Manley, R., Electrostatic Fiber Spinning from Polymer Melts. III. Electrostatic Deformation of a Pendant Drop of Polymer Melt. *J. Polym. Sci.: Polym. Phys. Ed.*, 1981. 19: p.933-940.
21. Jaeger, R., Bergshoef, M.M., Martin, C., Schonherr, H.; and Vancso, G.J., *Macromol. Symp.*, 1998. 127: p.141-150.
22. Zachariades, A.E., Porter, R.S., Doshi, J., Srinivasan, G., and Reneker, D.H., High Modulus Polymers: A Novel Electrospinning Process. *Polym. News*, 1995. 20: p.206-207.
23. Gibson, P., Schreuder-Gibson, H., Pentheny, C., Electrospinning technology: direct application of tailorable ultrathin membranes. *J. Coated Fabrics*, vol. 28, pp. 63, July (1998).

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

24. Schreuder-Gibson, H. L., Gibson, P., Hsieh, Y.-L. Process-properties study of melt blowing polyurethane for elastic military protective apparel garments. International Nonwovens Technical Conference, Baltimore, 244 (2001).
25. Krishnappa, Ravi V. N.; Sung, Changmo; Schreuder-Gibson, Heidi. Materials Research Society Symposium Proceedings, 702 (Advanced Fibers, Plastics, Laminates and Composites), 235 (2002).
26. Gibson, P. W.; Schreuder-Gibson, H. L.; Rivin, D. Electrospun fiber mats: transport properties. AIChE Journal, 45(1), 190 (1999).
27. Zong, X.; Kim, K.; Fang, D.; Ran, S.; Hsiao, B. S.; Chu, B. Structure and process relationship of electrospun bioabsorbable nanofiber membranes. Polymer, 43(16), 4403 (2002).

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HB Gao, DF Fang, FQ Lu et al, "Electron impact ionization cross section of Ar⁺, Kr⁺, In⁺ and Ge⁺", Nucl. Instr. & Methods B132, 364 (1997)

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

- H. Ma, W. Sh, B. Yan, Y. Li, D. Fang, F. Lu, J. Tang and F. Yang, "Optical isotope shifts in Nd II (26772)11/2 by collinear fast-ion-beam laser spectroscopy", J. Phys., B30, 3355 (1997)
- Ma Hongliang, Shi Wei, Yan Bin, Li Yong, Fang Dufei, Lu Fuquan, Tang Jiayong and Yang Fujia, "Optical isotope shifts in Nd II (25524) 13/2 using collinear fast-ion-beam laser spectroscopy", ACTA PHYSICA SINICA 6(9), 677 (1997)
- B. Yan, H. Ma, Z. Wang, D. Fang, S. Wu and F. Lu, "Single electron capture cross sections of C⁺, N⁺ and O⁺ impact on H₂ at the energy of 7.5 - 30 keV", J. Atomic and Nuclear Physics 14(2), 267 (1997)
- Ma Hongliang, Shi Wei, Chen Miaohua, Chen Zhijun, Fang Dufei, Lu Fuquan and Yang Fujia, "Optical isotope shifts in Nd II", J. Atomic and Nuclear Physics 15(7), 85 (1998)
- H. Ma, W. Shi, B. Yan, M. Chen, Z. Chen, D. Fang, F. Lu, J. Tang and F. Yang, "Changes in mean square nuclear charge radii in Nd from optical isotope shifts by collinear fast-ion-beam laser spectroscopy", Chinese Physics Letters 15(3) (1998)
- A.P. Graham, D. Fang, E.M. McCash and W. Allison, "Adsorption of atomic hydrogen on Cu(001) studied with helium-atom scattering", Physical Review B 57, 13158 (1998)
- B. Yan, Y. Li, H. Ma, D. Fang, S. Wu and F. Lu, "Measurement of single electron capture cross sections for Nd⁺ impact on H₂", J. Atomic and Nuclear Physics, 15(8), 196 (1998)
- Liguo Song, Dufei Fang, Robert K. Kobos, Salvatore J. Pace and Benjamin Chu, "Separation of dsDNA fragments in plastic capillary electrophoresis chips by using E99P69E99 as separation medium", Electrophoresis 20, 2847, (1999)
- S. Ran, S. Cruz, X. Zong, D. Fang, B. Chu and B. Hsiao, "Structure development during the heat-draw process of Nylon66 fiber by synchrotron X-ray diffraction", Advances in X-ray analysis - Proceedings from the 1999 Denver X-ray conference (1999)
- S. Ran, X.Zong, D. Fang, B. Hsiao and B. Chu, "Novel image analysis of two-dimensional X-ray fiber diffraction pattern: example of polypropylene fiber drawing study", J. Applied Crystallography 33, 1031 (2000)
- S. Ran, D. Fang, S. Zong, B. S. Hsiao, B. Chu, and P. M. Cunniff, "Structural Changes during Deformation of Kevlar Fibers via On-Line Synchrotron SAXS/WAXD Techniques", Polymer, 42(4), 1601-1612 (2000).
- S. Ran, X. Zong, D. Fang, B. S. Hsiao, B. Chu and R. A. Phillips, "Structural and Morphological Studies of Isotactic Polypropylene Fibers during Heat/Draw Deformation by in-situ Synchrotron SAXS/WAXD", Macromolecules, 34(8) 2569-2578 (2001).
- L.Song, D.Liang, Z.Chen, D. Fang and B.Chu "DNA sequencing by capillary electrophoresis using mixtures of polyacrylamide and poly(N,N-dimethylacrylamide)", J. Chromatography A. 915, 231 (2001)

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Associate Editor, Materials Letters, 1986-1989; Editorial Board, Journal of Colloid and Interface Science, 1986-1989; Editorial Advisory Board, Macromolecules, 1990-1992; Editorial Board, Review of Scientific Instruments, 1993-1995; Editorial Advisory Board, Journal of Polymer Science, Part B (Polymer Physics), 1990- .

Fellowships, Special Invitations and Honors:

Participant of the 1966 Study Week on Molecular Forces, Pontifical Academy of Science, Vatican City, Rome, Italy; Alfred P. Sloan Research Fellow, 1966-1968; John Simon Guggenheim Fellow, 1968-1969; Visiting Professor, Japan Society for the Promotion of Science (JSPS), 1975-1976,1992-1993; Humboldt Award for Senior U.S. Scientists, 1976-1977,1992-1993; Distinguished Achievement Award in Natural Science, St. Norbert College, 1981; Fellow, American Institute of Chemists; Fellow, American Physical Society; Honorary Professor of the Chinese Academy of Sciences, 1992- ; High Polymer Physics Prize, American Physical Society, 1993; Langmuir Distinguished Lecturer Award, Division of Colloid & Surface Chemistry, American Chemical Society, 1994.; Honorary Professor, Nankai University, 1996- ; Award for Distinguished Service in Advancement of Polymer Science, Society of Polymer Science, Japan, 1997; Honorary Professor, Xiamen University, 1998- ; Outstanding Achievement Award, Chinese Institute of Engineers/USA, 1998.

Publications: 472 scientific papers, 5 book reviews, 6 books, 7 patents, 2 meeting reports, 7 article reviews, and 18 papers in progress.

Five Relevant Publications:

Shaofeng Ran, Christian Burger, Dufei Fang, Xinhua Zong, Sharon Cruz, Benjamin Chu, Benjamin S. Hsiao, Robert A. Bubeck, Kazuyuki Yabuki, Yoshihiko Teramoto, David C. Martin, Michael A. Johnson and Philip M. Cuniff, "In-situ Synchrotron WAXD/SAXS Studies of Structural Development during PBO/PPA Solution Spinning," *Macromolecules*, **35**, 433-439 (2002).

Tianbo Liu, Quan Wan, Yi Xie, Christian Burger, Li-Zhi Liu and Benjamin Chu,

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

"Polymer-Assisted Formation of Giant Polymolybdate," *J. Am. Chem. Soc.*, **123**, 10966-10972 (2001).

Francisco J. Medellin-Rodriguez, Christian Burger, Benjamin S. Hsiao, Benjamin Chu, Richard Vaia and Shawn Phillips, "Time-Resolved Shear Behavior of End-Tethered Nylon 6-Clay Nanocomposites Followed by Non-Isothermal Crystallization," *Polymer*, **42**, 9015-9023 (2001).

Shaofeng Ran, Xinhua Zong, Dufei Fang, Benjamin S. Hsiao, Benjamin Chu, Philip M. Cunniff and Roger A. Phillips, "Studies of the Mesophase Development in Polymeric Fibers during Deformation by Synchrotron SAXS/WAXD," *J. Mat. Sci. Papers*, **36**, 3071-3077 (2001).

Shaofeng Ran, Xinhua Zong, Dufei Fang, Benjamin S. Hsiao, Benjamin Chu and Roger A.

Phillips, "Structural and Morphological Studies of Isotactic Polypropylene Fibers during Heat/Draw Deformation by in-Situ Synchrotron SAXS/WAXD," *Macromolecules*, **34**, 2569-2578 (2001).

Five Additional Related Publications:

Benjamin S. Hsiao and Benjamin Chu, "Scattering: Light, Neutrons and X-Rays," in *Encyclopedia of Chemical Physics and Physical Chemistry, Vol. II: Methods*, eds. J. H. Moore and N. D. Spencer, IoP Publishing Ltd., Philadelphia, PA, Section B1.9, pp.1197-1225 (2001).

Benjamin Chu and Benjamin S. Hsiao, "Small-Angle X-Ray Scattering of Polymers", *Chem. Rev.*, **101**, 1727-1761 (2001).

Shaofeng Ran, Dufei Fang, Xinhua Zong, Benjamin S. Hsiao, Benjamin Chu and Philip M. Cunniff, "Structural Changes during Deformation of Kevlar Fibers via On-line Synchrotron SAXS/WAXD Techniques," *Polymer*, **42**, 1601-1612 (2001).

Shaofeng Ran, Xinhua Zong, Dufei Fang, Benjamin S. Hsiao, Benjamin Chu and Roger Ross, "Novel Image Analysis of Two-Dimensional X-Ray Fiber Diffraction Patterns: Example of a Polypropylene Fiber Drawing Study," *J. App. Cryst.*, **33**, 1031-1036 (2000).

Shuiqin Zhou and Benjamin Chu, "Assembled Materials: Polyelectrolyte-Surfactant Complexes," *Advanced Materials*, **12**, 545-556 (2000).

Biographical Sketch: Benjamin S. Hsiao

A. Vitae

Address: Chemistry Department Phone: (516)632-7793
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www: <http://bh03.chem.sunysb.edu>
Birth Date: August 12, 1958 Citizenship: U.S.

Education:
1987 Ph.D., Materials Science (Polymer Science), University of Connecticut
1984 M.S., Materials Science (Polymer Science), University of Connecticut
1980 B.S., Chemical Engineering, National Taiwan University

Professional Positions:

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

- 2002-present Professor, State University of New York at Stony Brook
- 1998-2002 Associate Professor, State University of New York at Stony Brook
- 1997-1998 Assistant Professor, State University of New York at Stony Brook
- 1997-present Spokesperson, Advanced Polymers PRT (X27C beamline) at NSLS, BNL
- 1994-2001 Adjunct Associate Professor, Materials Science, University of Delaware
- 1994-1997 Alternative Member of the DND-CAT (DuPont-Northwestern-Dow Collaborative Access Team) Management Board, APS, ANL
- 1989-1997 Staff Scientist, Fibers; Central Research & Development, Experimental Station, E. I. du Pont de Nemours & Co.
- 1987-1989 Post-Doctoral Research Fellow, Dept. Polymer Sci. Eng., University of Massachusetts

Professional Activities:

Member of Editorial Advisory Board for *J. Macromol. Sci. - Phys.*; *J. Polym. Research*; *High Performance Polymers*; *Chinese J. Applied Chemistry*
 Proposal and Panel Reviewer for NSF, ACS-PRF, DOD, DOE, NSLS, SSL (Synchrotron), NIST, BNL
 Consultant: DuPont, Dow Chemical, Ethicon Inc., ExxonMobil, Fellowes
 Program Committee for APS Workshop on Polymer Scattering (1994), NSLS User Workshop (1996), Denver X-ray Conference (1997), ACS-PMSE Symposium "Scattering from Polymers" (1998, 2001), Chair, SAS-SIG, ACA (1999), XI International SAS Conference at Brookhaven National Lab (1999)
 Professional Societies: American Chemical Society; American Crystallographic Association; American Physical Society; Materials Research Society; American Association for the Advancement of Science

Honors and Awards:

Sigma Xi; Phi Kappa Phi; University of Connecticut Doctoral Fellowship (1985); Two SPE-ANTEC Best Technical Papers (1992); DuPont Young Faculty Award (1998-2000); Guest Professor in Changchun Institute of Chemistry, Chinese Academic of Sciences

B. Publications.

(134 referred publications, 20 pending publications, 85 conference proceedings, 6 patent applications and 1 book)

Five Publications Most Related to the Project:

- b. J. M. Samon, J. M. Schultz, B. S. Hsiao, S. Seifert, N. Stribeck, I. Gurke, C. Saw and G. Collins, "Structure Development during the Melt Spinning of Polyethylene and Poly(vinylidene) Fibers by in-situ Synchrotron Small- and Wide-Angle X-ray Scattering Techniques", *Macromolecules*, 32(24), 8121-8132 (1999).
- c. S. Ran, D. Fang, S. Zong, B. S. Hsiao, B. Chu, and P. M. Cunniff, "Structural Changes during Deformation of Kevlar Fibers via On-Line Synchrotron SAXS/WAXD Techniques", *Polymer*, 42(4), 1601-1612 (2000).
- d. R. H. Somani, B. S. Hsiao, A. Nogales, S. Srinivas, A. H. Tsou, I. Sics, F. J. Balta-Calleja, and T. A. Ezquerro, "Structure Development during Shear Flow Induced Crystallization of iPP: In-situ Small Angle X-ray Scattering Study", *Macromolecules*, 33(25), 9385-9394 (2000).
- e. Bruce X. Fu, Ling Yang, Rajesh H. Somani, Steven X. Zong, Benjamin S. Hsiao, Shawn Phillips, Rusty Blanski and Patrick Ruth "Crystallization Studies of Isotactic Polypropylene Containing Nanostructured Polyhedral Oligomeric Silsesquioxanes (POSS) Molecules under Quiescent and Shear Conditions", *J. Polym. Sci. Polym. Phys.*, 39(22), 2727-2739 (2001).
- f. S. Ran, X. Zong, D. Fang, B. S. Hsiao, B. Chu and R. A. Phillips, "Structural and Morphological Studies of Isotactic Polypropylene Fibers during Heat/Draw Deformation by in-situ Synchrotron SAXS/WAXD", *Macromolecules*, 34(8) 2569-2578 (2001).

Five Additional Significant Publications:

- B. S. Hsiao, B. B. Sauer, R. Verma, B. Chu, P. Harney, H. G. Zachmann and S. Seifert, "New Insight of Isothermal Melt Crystallization Via Time-Resolved Simultaneous SAXS/WAXD Measurements", *Macromolecules*, 28, 6931-6936 (1995).

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

- L. Zhu, S. Z. D. Cheng, B. H. Calhoun, Q. Ge, R. P. Quirk, E. T. Thomas, B. S. Hsiao, F. J. Yeh and B. Lotz, "Crystallization Temperature-Dependent Crystal Orientations within Nanoscale Confined Lamellae of a Self-Assembled Crystalline-Amorphous Diblock Copolymer", J. Am. Chem. Soc., 122(25), 5957-5967 (2000).
- Z. G. Wang, B. S. Hsiao, E. B. Sirota, P. Agarwal and S. Srinivas, "Probing the Early Stages of Polymer Crystallization by Simultaneous Small- and Wide-Angle X-ray Scattering", Macromolecules, 33(3), 978-989 (2000).
- C. Park, S. Simmons, L. J. Fetters, B. Hsiao, F. Yeh and E. L. Thomas, "Spherical to Cylindrical Microdomain Transformation by Application of a Flow Field", Polymer, 41(8), 2971-2977 (2000).
- Zhi-Gang Wang, Xuehui Wang, Benjamin S. Hsiao, Roger A. Phillips, Francisco J. Medellin-Rodriguez, Srivatsan Srinivas, Charles C. Han, "Structure and Morphology Development in Syndiotactic Polypropylene during Isothermal Crystallization and Subsequent Melting", J. Polym. Sci, Polym. Phys., 39 (23), 2982-2995 (2001).

C. Collaborators within the Past 48 Months - other than on the Listed Publications.

Francisco Baltá-Calleja, Stephen Z. D. Cheng, Benjamin Chu, Julia Kornfield, Joe Lichtenhan, Sanjeeva Murthy, M. Muthukumar, Roger Phillips, Miriam Rafailovich, Rick Register, Jim Runt, Hong J. Sue, Bryan B. Sauer, Jerold M. Schultz, Richard S. Stein, Norbert Stribeck, Edwin L. Thomas, Andy Tsou, Jack Zhou

Current Graduate Students and Postdoctoral Fellows.

Graduate Students: Steven X. Zong, Bruce X. Fu, Ling Yang, Meiki Yu, Jonathan Chiu

Postdoctorals and Visiting Scientists: Fengji Yeh (97-), Zhigang Wang (97-), Lizhi Liu (97-), DuFei Fang (97-), Shaofeng Ran (98-), KwanSok Kim (00-), Raj Somani (99-), Michael Gelfer (00-), Igors Sics (00-), Shigeyuki Toki (01-), Daisuke Kawakami (01-)

Graduate and Postdoctoral Advisors.

Graduate Advisors: Montgomery T. Shaw and Edward T. Samulski

Postdoral Advisors: Richard S. Stein and H. Henning Winter

BENJAMIN CHU - RESEARCH SUPPORT (TOTAL COST)

ACTIVE

1.	2 R01 HG01386-07 (Chu) National Institutes of Health Separation Media for DNA Capillary and Micro-Chip Based Electrophoresis	9/01/01 – 8/31/04 \$811,026	10%
2.	DAAD19011-394 DoD ARO-DURIP (PI: Chu; Co-PI: Hsiao) Micro-Processing System for Lightweight Flexible Nanocomposites	04/01/01-03/31/02 \$78,850 (including \$23,655 in matching funds)	5%
3.	DMR 9984102 (Chu)	1/1/00 – 12/31/02	10%

Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

National Science Foundation Nanostructures and Activity of Polyelectrolyte/ Surfactant Complexes	\$285,000	
4. DAAD 190010419 (Chu) U.S. Army Research Office Dynamic Studies in Fiber Processing (SUNY/Stony Brook)	7/01/00 – 6/30/03 \$347,160	10%
5. DEFG0286ER45237.016 Department of Energy (Chu) Modification of Nanostructured Materials	1/1/01 – 12/31/03 \$338,968	10%
6. DEFG0299ER45760 (Hsiao, PI; Chu, Co-PI) Department of Energy Support for the Advanced Polymers Beamline at the National Synchrotron Light Source	3/15/99 – 3/14/02 \$300,000	5%
7. CARS: A National Chemistry and M National Science Foundation (PI: J. P. Viccaro) ChemMat aterials Synchrotron Research Facility at the Advanced Photon Source (APS) (Co-PIs: B. Chu, P. Coppens, S. Rice, M. Schlossman, P. S. Pershan).	\$5,563,166 3/15/01 – 2/28/06 (includes of supplement of \$240,000 per year from DoE)	5%
8. National Science Foundation (PI: M. Rafailovich) MRSEC for Polymers at Engineered Interfaces (Co-PIs: B. Chu, J. Sokolov, B. Hsiao, D. Gersappe);	6/01/01 – 5/31/06 \$4,093,283	5%
9. NIH-SBIR (PI: Dufei Fang; Co-PIs: B. Chu/B.Hsiao) Bioabsorbable Nanostructured Membranes for Prevention of Post-Operative Adhesions	05/01/01-04/30/03 \$399,294	5%
10. Center for Biotechnology (Co-PI: B. Chu) Fabrication of Bioabsorbable Membranes For Prevention of Post-Operative Adhesions	07/01/01-06/15/02 \$35,000	5%

RESEARCH SUPPORT (TOTAL COST)

PI: BENJAMIN S. HSIAO

ACTIVE

1. Clemson University Research Foundation (Hsiao) (as subcontractor on their NSF grant) In-Situ X-Ray Studies of Polymer Fiber/Film Deformation	5/1/00 – 9/30/02 \$122,500	5%
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Unique Hybrid Multi-Jet Electrospinning and Melt-Blown Technology for Mass Production of Nanostructured Membranes

2.	Center for Biotechnology (Co-PI: B. Chu) Fabrication of Bioabsorbable Membranes For Prevention of Post-Operative Adhesions	07/01/01-06/15/02 \$35,000	5%
3.	DEFG0299ER45760 (Hsiao, PI; Chu, Co-PI) Department of Energy Support for the Advanced Polymers Beamline at the National Synchrotron Light Source	3/15/99 – 3/14/02 \$300,000	10%
4.	ExxonMobil Chemical Company (Hsiao) Flow Induced Crystallization in Polymers	2/15/00 – 2/14/03 \$181,000	10%
5.	National Institute of Standards & Technology (Hsiao) Characterization and modeling of Phase Separation and Crystallization of Polefin Blends	09/16/00-09/15/03 \$187,157	5%
6.	National Science Foundation (PI: M. Rafailovich) MRSEC for Polymers at Engineered Interfaces (Co-PIs: B. Chu, J. Sokolov, B. Hsiao, D. Gersappe);	6/01/01 – 5/31/06 \$4,093,283	5%
7.	National Science Foundation (Hsiao) Orientation-Induced Crystallization in Polymers	04/01/01-03/31/04 \$328,577	10%
8.	DoD ARO-DURIP (PI: Chu; Co-PI: Hsiao) Micro-Processing System for Lightweight Flexible Nanocomposites	04/01/01-03/31/02 \$78,850 (including \$23,655 in matching funds)	5%
9.	NIH-SBIR (PI: Dufei Fang; Co-PIs: B. Chu/B.Hsiao) Bioabsorbable Nanostructured Membranes for Prevention of Post-Operative Adhesions	05/01/01-04/30/03 \$399,294	5%

EXHIBIT B



US006689374B2

(12) **United States Patent**
Chu et al.(10) **Patent No.:** **US 6,689,374 B2**
(45) **Date of Patent:** **Feb. 10, 2004**(54) **BIODEGRADABLE AND/OR
BIOABSORBABLE FIBROUS ARTICLES AND
METHODS FOR USING THE ARTICLES FOR
MEDICAL APPLICATIONS**(75) **Inventors:** **Benjamin Chu, Setauket, NY (US);
Benjamin S. Hsiao, Setauket, NY (US);
Dufei Fang, Painted Post, NY (US);
Collin Brathwaite, Setauket, NY (US)**(73) **Assignee:** **The Research Foundation of State
University of New York, Stony Brook,
NY (US)**(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) **Appl. No.:** **10/375,329**(22) **Filed:** **Feb. 27, 2003**(65) **Prior Publication Data**

US 2003/0228350 A1 Dec. 11, 2003

Related U.S. Application Data(62) Division of application No. 09/859,007, filed on May 16,
2001.(51) **Int. Cl.⁷** **A61F 2/02**(52) **U.S. Cl.** **424/423; 424/424; 424/425;
424/426**(58) **Field of Search** **424/423, 424,
424/425, 426**(56) **References Cited****U.S. PATENT DOCUMENTS**

3,975,565 A	8/1976	Kendall
4,043,331 A	8/1977	Martin et al.
4,323,525 A	4/1982	Bornat
4,345,414 A	8/1982	Bornat et al.
4,468,922 A	9/1984	McCraday et al.

4,689,186 A	8/1987	Bornat
4,810,180 A	3/1989	Isner
4,840,626 A	6/1989	Linsky et al.
4,878,908 A	11/1989	Martin et al.
4,911,867 A	3/1990	Burlet et al.
5,066,755 A	11/1991	Lemstra
5,296,172 A	3/1994	Davis et al.
5,480,436 A	1/1996	Bakker et al.
5,508,036 A	4/1996	Bakker et al.
5,569,528 A	10/1996	Van der Loo et al.
5,714,159 A	2/1998	Shalaby
5,783,111 A	7/1998	Ikkala et al.
5,795,584 A	8/1998	Totakura et al.

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

WO	WO98/03267	1/1998
WO	WO01/26610 A1	4/2001
WO	WO01/27365 A1	4/2001

OTHER PUBLICATIONSDzenis et al, "Polymer Hybrid Nano/Micro Composites,"
Proceedings of the American Society for Composites =
Ninth technical Conference, pp. 657-665.*

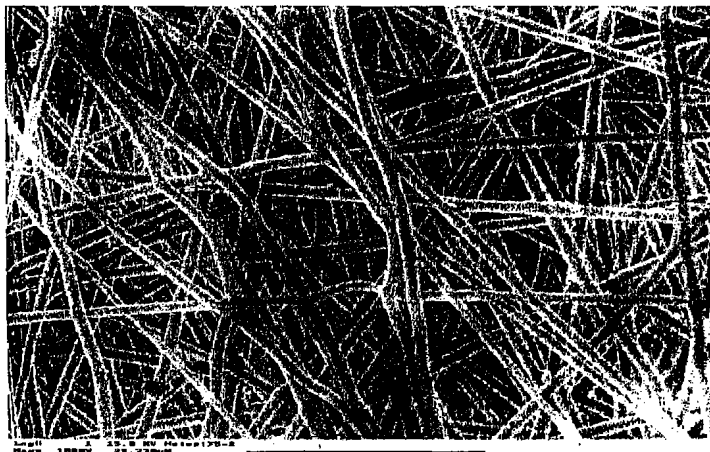
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Primary Examiner—Carlos Azpuru(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57)

ABSTRACT

Biodegradable and/or bioabsorbable fibrous articles and methods for using the articles in medical applications are disclosed. The biodegradable and/or bioabsorbable fibrous articles, which are formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, comprise a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. Articles having specific medical uses include an adhesion-reducing barrier and a controlled delivery system. The methods include methods for reducing surgical adhesions, controlled delivery of a medicinal agent and providing controlled tissue healing.

29 Claims, 13 Drawing Sheets

U.S. PATENT DOCUMENTS

6,010,692	A	1/2000	Goldberg et al.
6,013,371	A	1/2000	Hager et al.
6,037,331	A	3/2000	Shalaby et al.
6,056,970	A	5/2000	Greenawalt et al.
6,060,582	A	5/2000	Hubbell et al.
6,090,910	A	7/2000	Shinoda et al.
6,106,913	A	8/2000	Scardino et al.
6,218,441	B1	4/2001	Meluch et al.

OTHER PUBLICATIONS

Dzenis et al., "Polymer Hybrid Nano/Micro Composites," *Proceedings of the American Society for Composites—Ninth Technical Conference*, pp. 657–65 (1994).
Bezwała et al., "Poly(p-Dioxanone) and Its Copolymers," *Handbook of Biodegradable Polymers*, # 29–61 (1997).

* cited by examiner

FIG-1

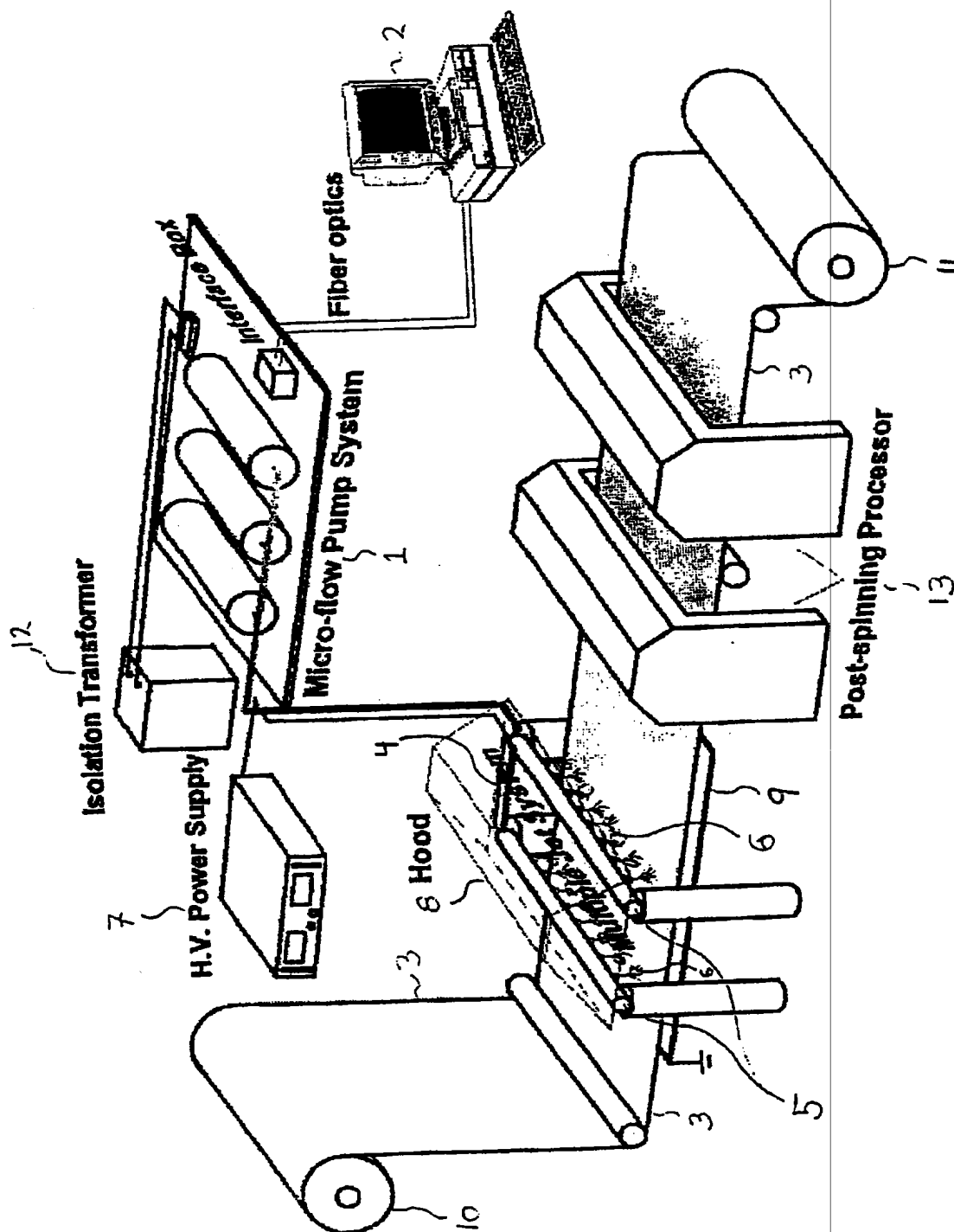
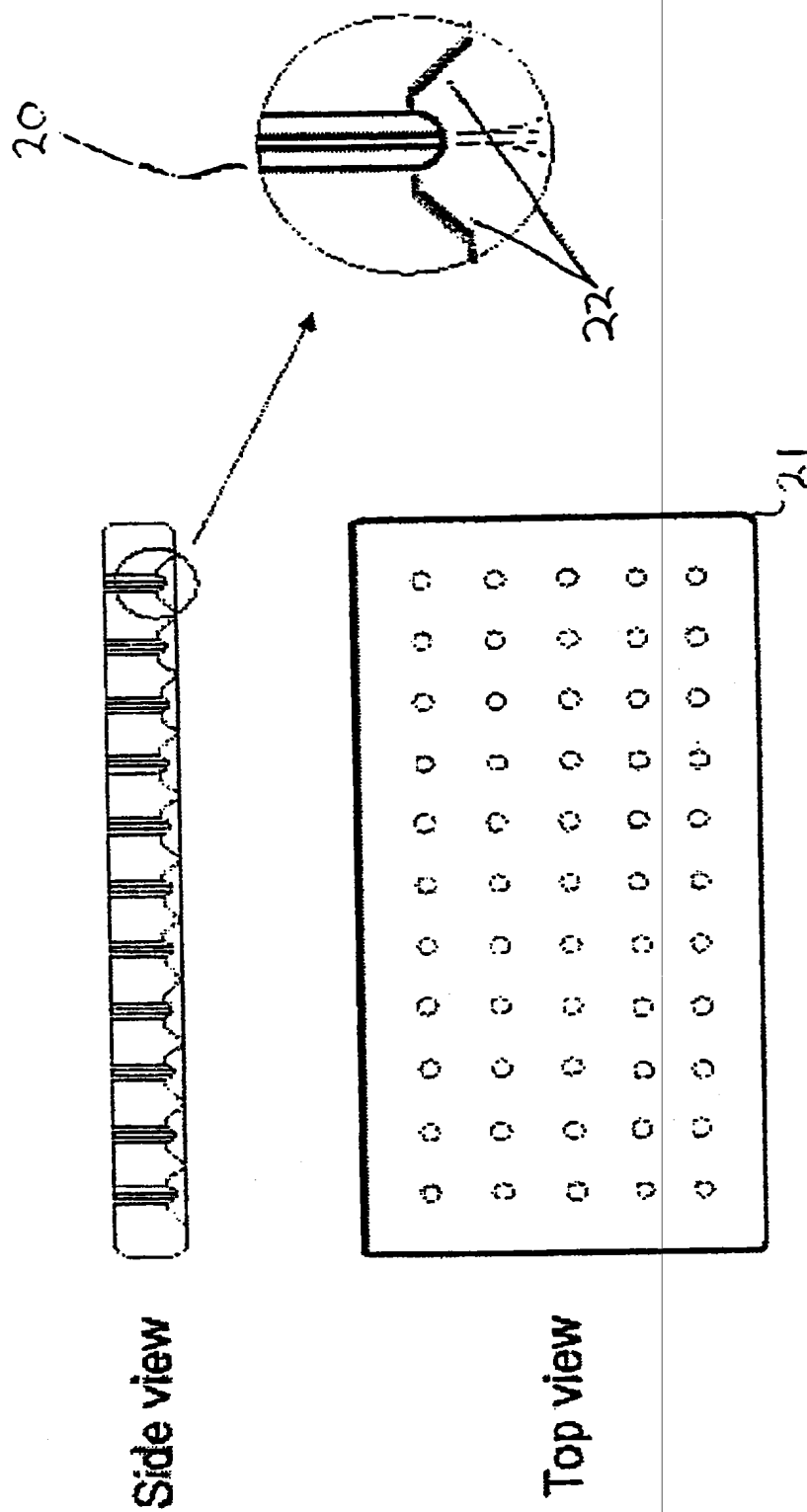


FIG-2



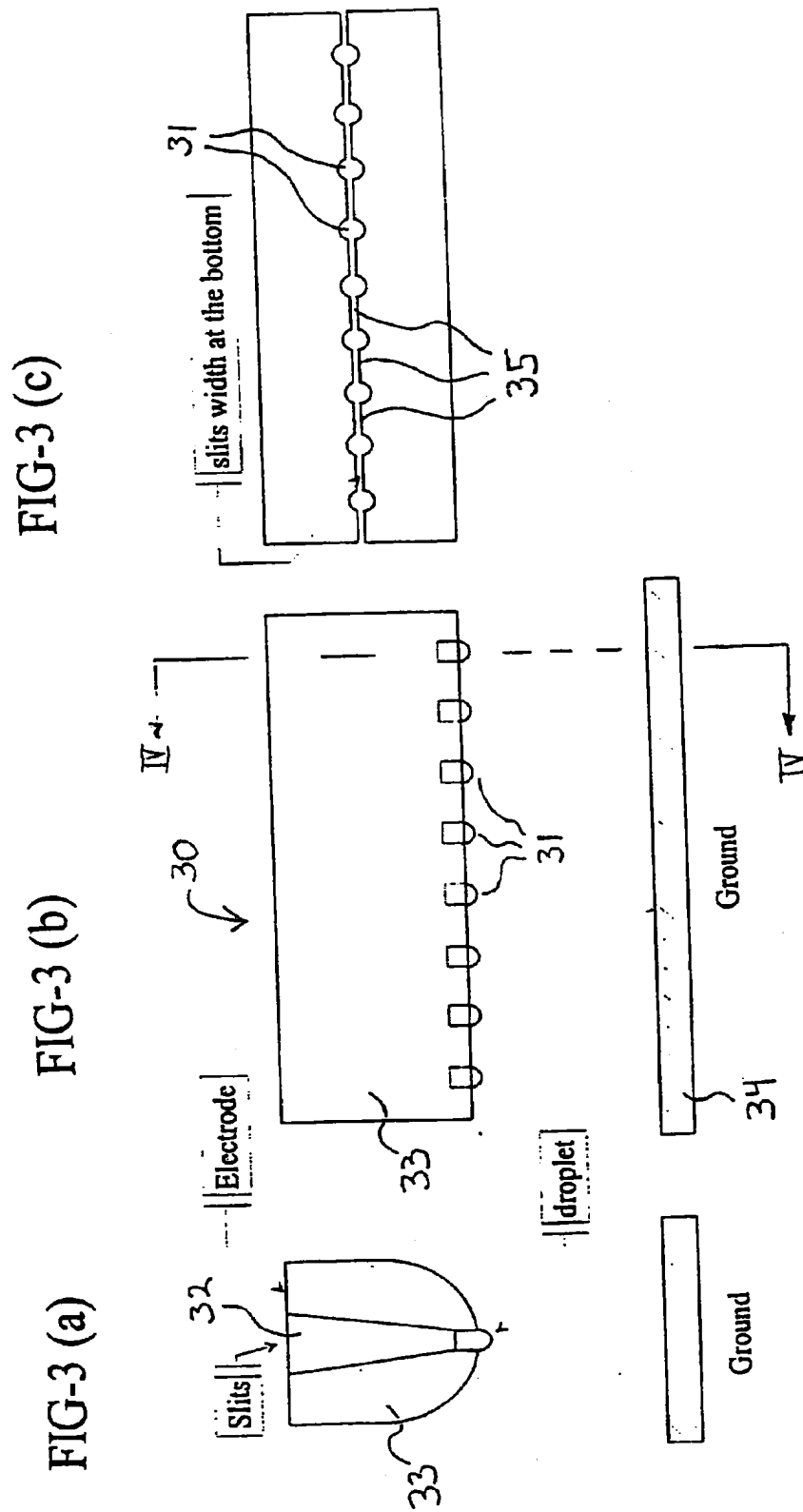


FIG-5

Spun membrane without salt

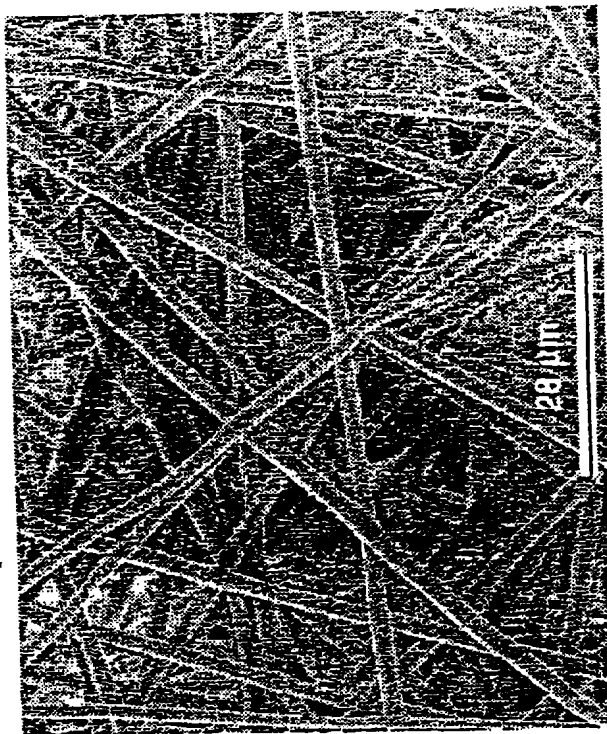


FIG-4

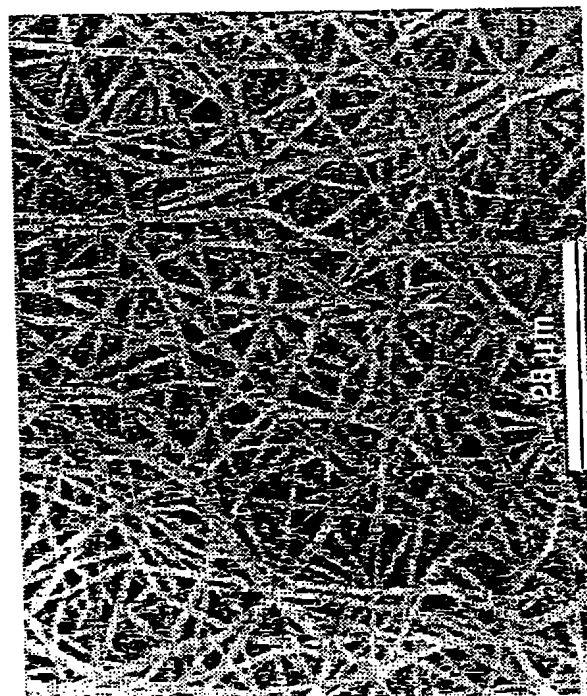
Spun membrane with 1 wt% KH_2PO_4 

FIG-6

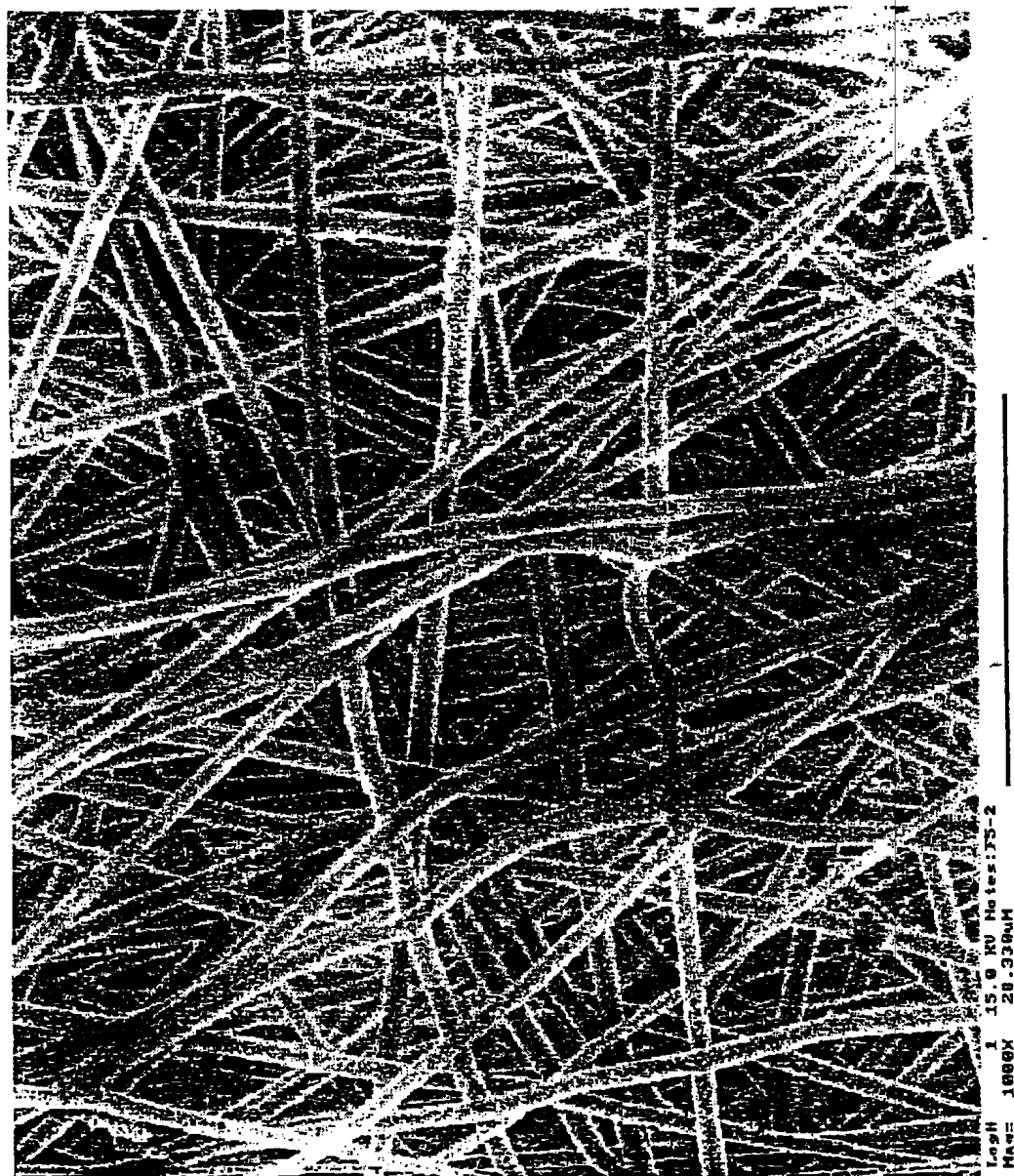


FIG-7

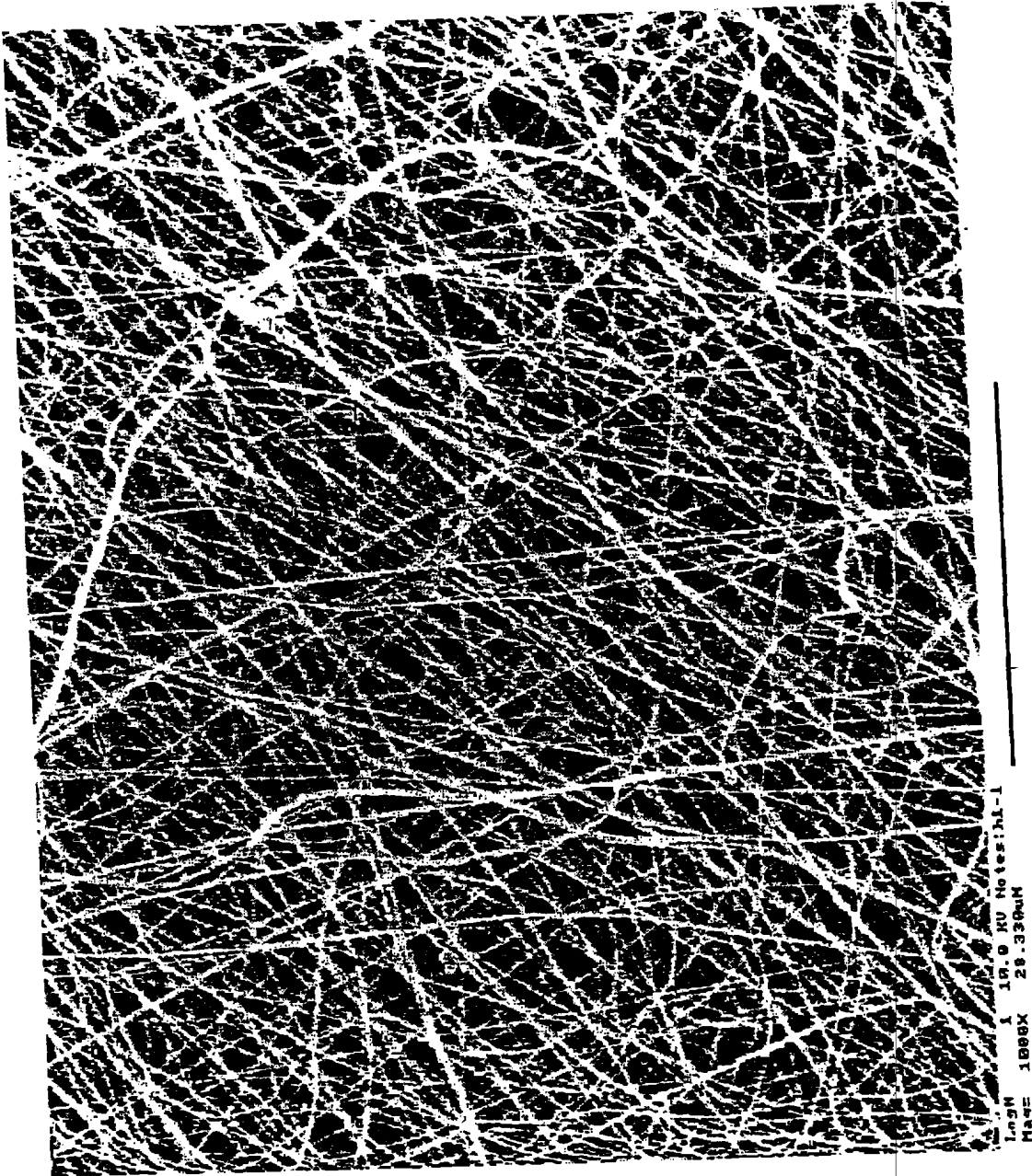
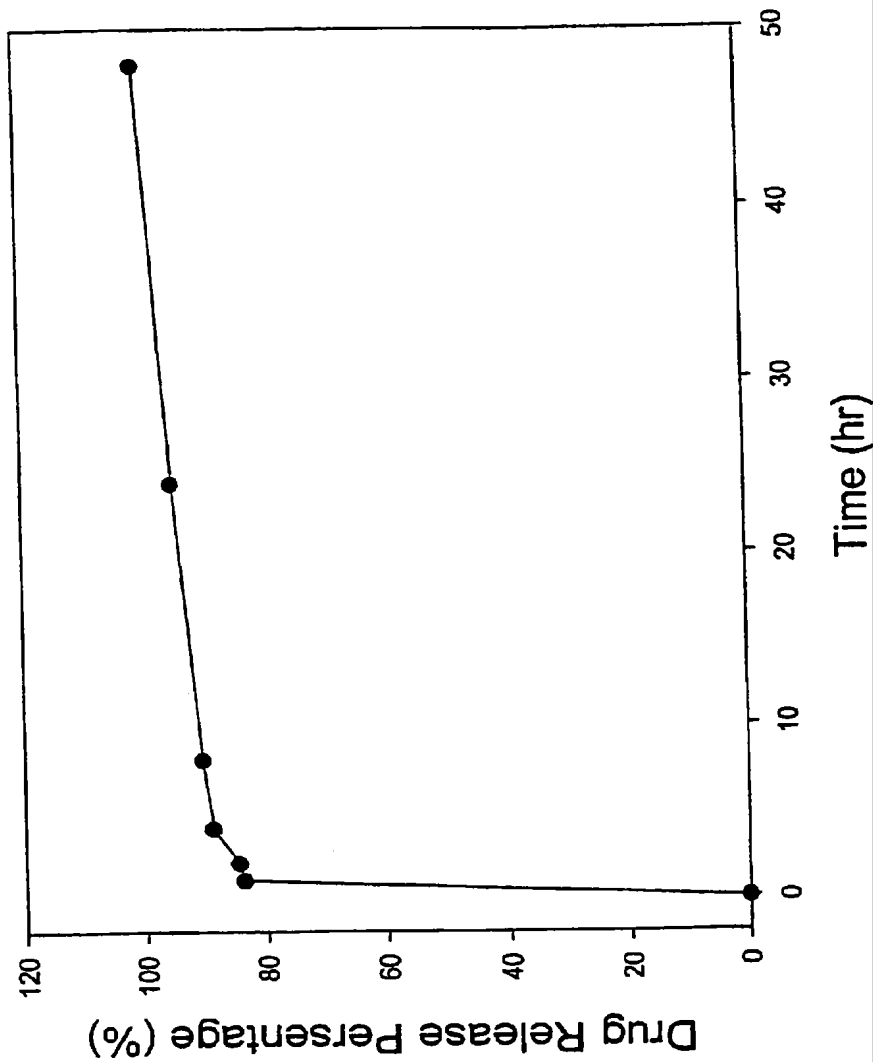


FIG-8



In Vitro Drug Release Profile

FIG-10

Biodegradation rate of electrospun membr

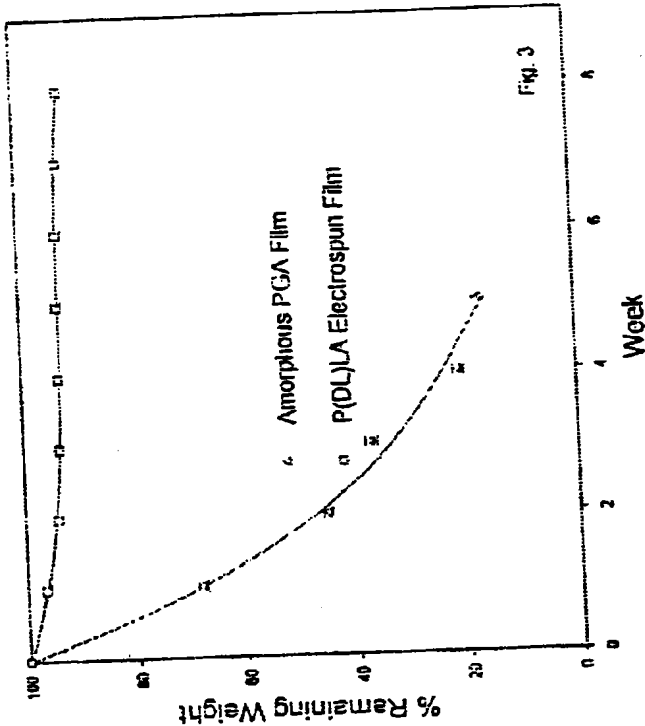


FIG-9

SEM image of electrospun PLAmembrane

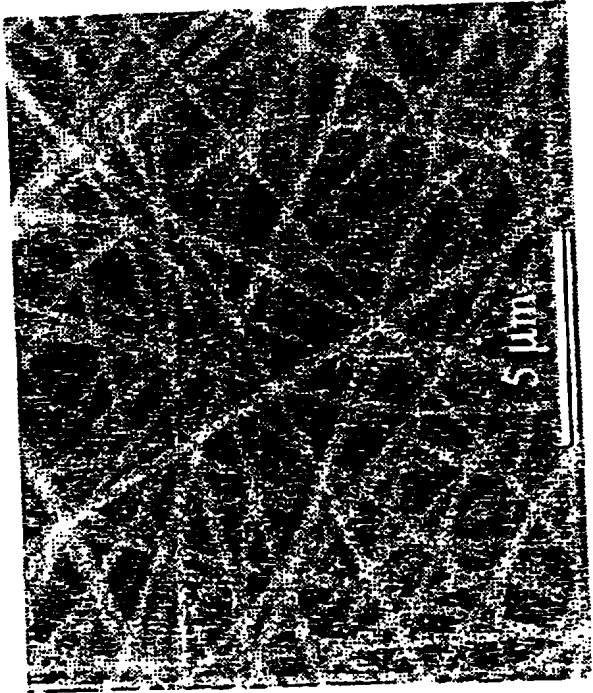


FIG-12

Membrane after 1 week of degradation



FIG-11

Dual thickness PLA membrane



FIG-13

Incidence of Adhesion

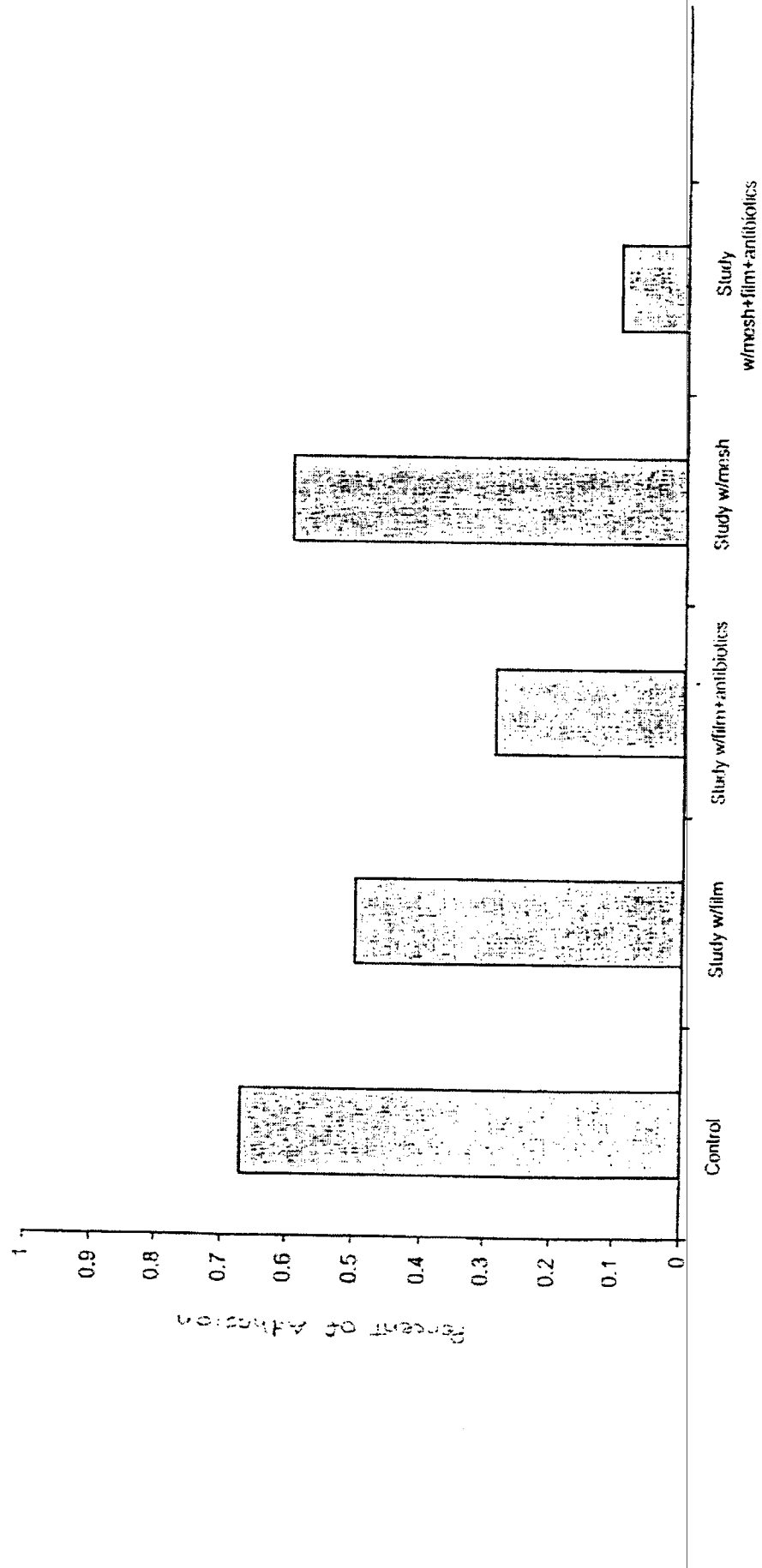


FIG-14

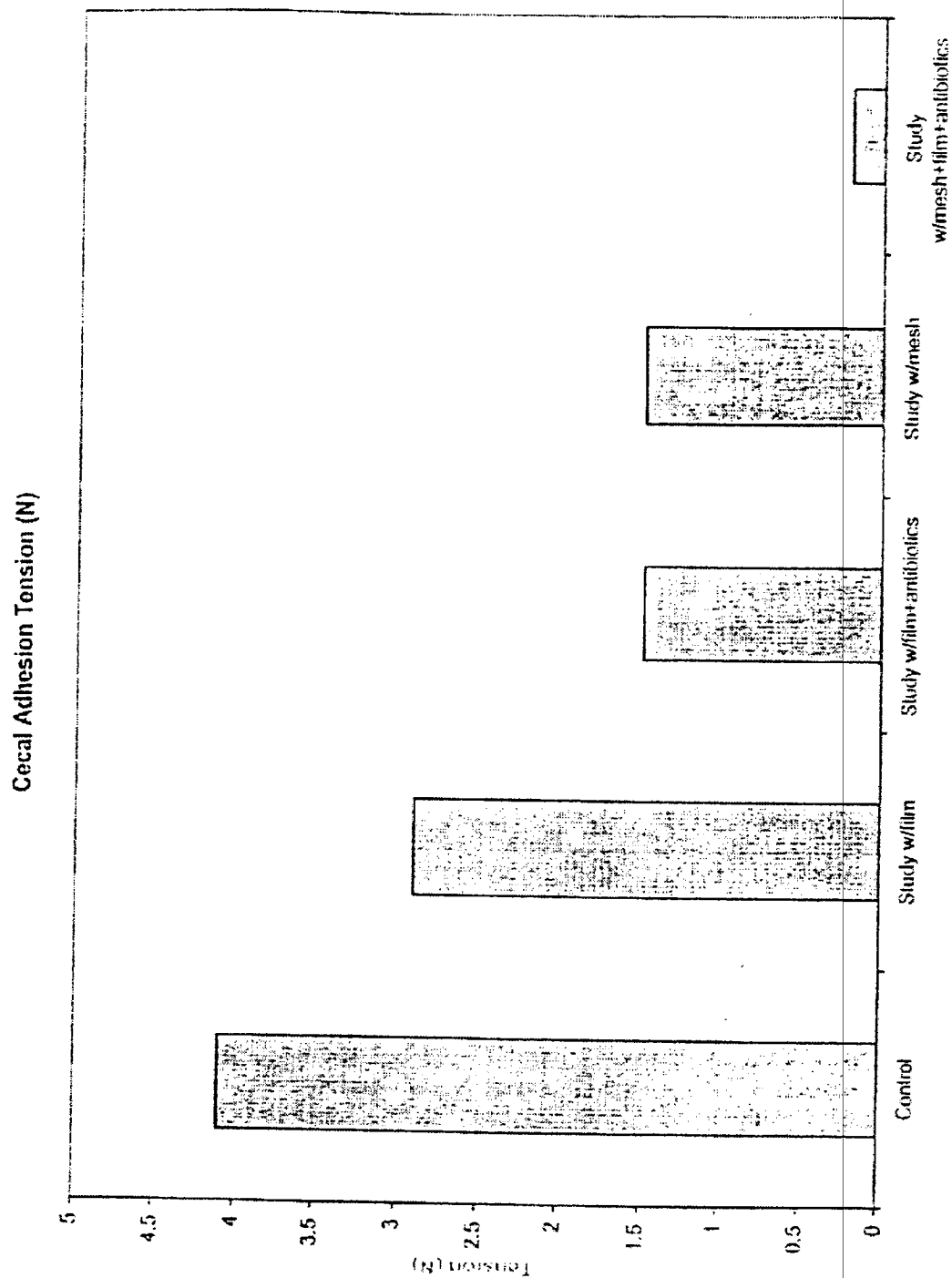


FIG-15
Antibacterial test results of PLA membrane

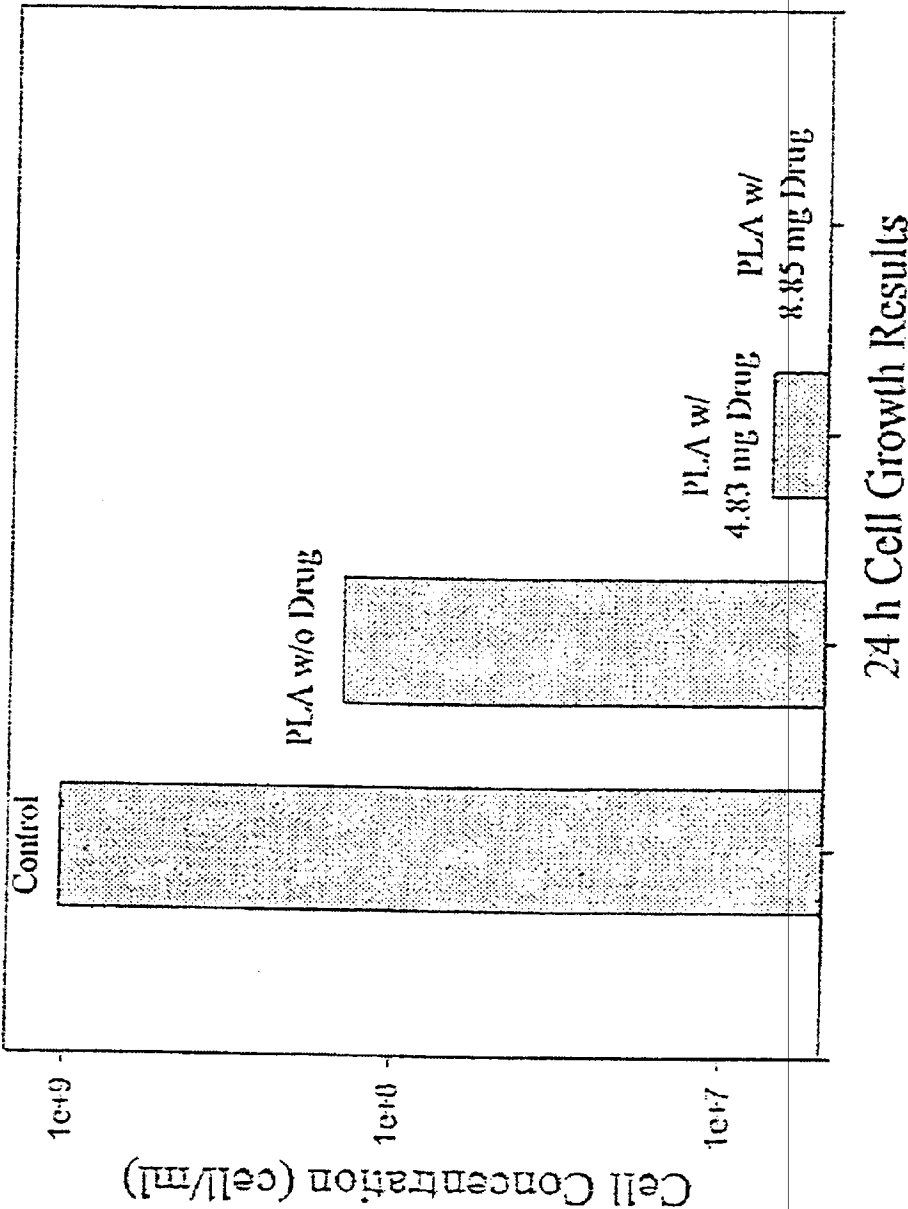


FIG-16

SEM image of as-spun membrane

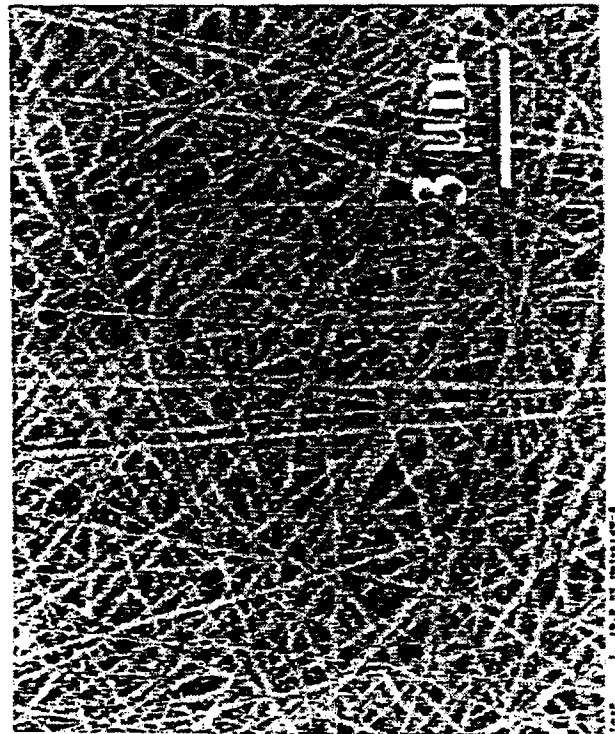
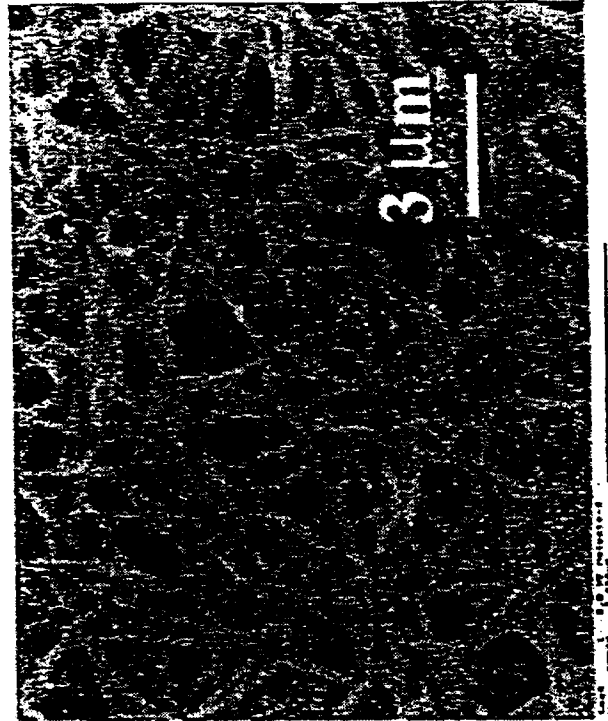


FIG-17

In-vivo degradation after a week

1

BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS

This application is a Divisional of Ser. No. 09/859,007 filed on May 16, 2001.

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fibrous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of inde-

2

pendently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokim) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-

fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminoglycan can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning

fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

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In one embodiment, the above described fibrous articles are in the form of a membrane.

The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the composite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for

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medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegradation rate with utility in a controlled delivery system.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic of an electrospinning system.

FIG. 2 is a schematic of an array of spinnerets for an electrospinning process.

FIG. 3(a) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. 3(b) is a cross-sectional view of the spinneret system of FIG. 3(a) as seen along viewing lines IV—IV thereof.

FIG. 3(c) is a bottom view of the multiple spinneret system of FIG. 3(a).

FIG. 4 is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4 .

FIG. 5 is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. 6 is an SEM of a membrane described in Example 1.

FIG. 7 is an SEM of a membrane described in Example 4.

FIG. 8 is a graph of the results of the drug release test described in Example 4.

FIG. 9 is an SEM of a PLA membrane described in Example 5.

FIG. 10 is a graph of the results of the biodegradation tests described in Example 6.

FIG. 11 is an SEM of the PLA membrane described in Example 7.

FIG. 12 is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. 13 is a graph of the results of the adhesion experiment described in Example 8.

FIG. 14 is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. 15 is a graph of the results of the antibacterial test described in Example 9.

FIG. 16 is an SEM of the as spun membrane described in Example 10.

FIG. 17 is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning

fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29-61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is

no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include poly-lactides, poly-glycolides, polycaprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers

having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000 nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorbable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth

factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorbable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between

muscle tissue and bone; barriers between the esophagus and mediasternum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioab-

sorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsorbable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6 . If the extrudate (conducting fluid) from each spinneret has a rate of about 10 $\mu\text{l}/\text{min}$, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4 , K_2HPO_4 , KIO_3 , KCl, MgSO_4 , MgCl_2 , NaHCO_3 , CaCl_2 , or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. 1. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. 1, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system 1. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4 . Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system 1 is linked to a computer 2 which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane 3 and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system 1 feeds the conducting fluid to a multiple jet system 4 that contains manifolds 5 having a bank of spinnerets 6. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply 7. A hood 8 is positioned over the multiple jet system 4 to remove the solvent at a controlled evaporation rate.

A ground plate 9 is positioned below the multiple jet system 4 such that an electric field is created between the charged spinnerets 6 and the ground plate 9. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate 9, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support 3 is positioned between the charged spinnerets 6 and the ground plate 9 to collect the fibers which are formed from the spinnerets and to form an interconnected web of the fibers. The support 3 moves in the direction from the unwind roll 10 to the rewind roll 11.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer 12.

The post-spinning processors 13 have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed on May 16, 2001 and incorporated herein for all purposes by reference.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magnetohydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual

spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another method for producing membranes according to the present invention, reference will be made to FIG. 2. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets 20. The array of electrospinning spinnerets are assembled in a matrix 21 that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes 22. The spinneret 20 and the scanning electrodes 22 are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret 20 can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret 20 can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. 3(a)-3(c). In this apparatus, a multiple jet system 30 comprises an array of electrospinning spinnerets 31, each spinneret 31 being defined by a slit 32 formed in a slit-die 33 that is coupled to high voltage to serve as an electrode disposed above the ground plate 34. As shown in detail in FIG. 3(c), the spinnerets 31 are each interconnected by selectively

narrow slits 35, such that each spinneret 31 is interconnected to a neighboring spinneret 31 by a slit 35. The conducting fluid will not flow through the slits 35, but will flow through each of the spinnerets 31 in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate Through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. 4) than the one with no salt added (FIG. 5). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4 , KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55-0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20

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needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. 6.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorbable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the

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polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. 7.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 nm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. 8.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. 9 shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm³, as compared to the neat resin (PLA) density of 1.3 g/cm³.

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. 10. A review of FIG. 10 reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 μ l/min to 70 μ l/min. An SEM of the resulting membrane is shown in FIG. 11.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared

(FIG. 12). A comparison of FIGS. 11 and 12 reveals that this morphology results in a rapid weight loss in the first week. Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ -radiation doses from 5.15–25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylazine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A 1x1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned are (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibodies (see FIG. 13). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. 14). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while

10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1x1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10). All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesional strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0x7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. 15, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. 15 reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conducted using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug

ration of 9:1. A 20 kV positive voltage was applied to the electrode. An SEM of the initial as spun membrane (FIG. 16) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. 17.

A comparison of FIGS. 16 and 17 reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A system for controlled delivery of a medicinal agent comprising a medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with said medicinal agent to release said agent at a controlled rate, said fibrous article comprising a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

2. A system according to claim 1, wherein different fibers refers to fibers of different diameters.

3. A system according to claim 2, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.

4. A system according to claim 3, wherein said fibrous article comprises at least about 20 weight percent of sub-micron diameter fibers.

5. A system according to claim 4, wherein said fibrous article comprises at least about 50 weight percent of sub-micron diameter fibers.

6. A system according to claim 1, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

7. A system according to claim 1, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

8. A system according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

9. A system according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

10. A system according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

11. A system according to claim 10, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

12. A system according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

13. A system according to claim 1, wherein said fibers have diameters in the range from about 10 up to 1,000 nanometers.

14. A system according to claim 13, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

15. A system according to claim 1, further comprising small blobs of biodegradable and/or bioabsorbable material.

16. A system according to claim 1, further comprising at least one medicinal agent.

17. A system according to claim 16, wherein said medicinal agent is contained within said fibers.

18. A system according to claim 17, further comprising fibers with different concentrations of said medicinal agent.

19. A system according to claim 17, further comprising fibers with different medicinal agents.

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20. A system according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers.

21. A system according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

22. A system according to claim 1, wherein said fibrous article has a controlled degradation rate.

23. A system according to claim 1, wherein said fibrous article is a membrane.

24. A system according to claim 23, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

25. A system according to claim 24, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

26. A method for controlled delivery of a medicinal agent which comprises implanting at a target site in an animal, a

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system for controlled delivery of a medicinal agent, said system comprising a medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with said medicinal agent to release said agent at a controlled rate, wherein said article comprises a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

27. A method according to claim 26, wherein different fibers refers to fibers of different diameters.

28. A method according to claim 26, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

29. A method according to claim 26, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,689,374 B2
DATED : February 10, 2004
INVENTOR(S) : Chu et al.

Page 1 of 1

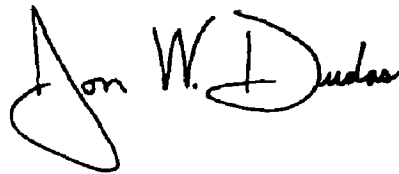
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1.

Line 5, after the title, insert -- This invention was made with government support under Grant Nos. DMR 9984102 and DMR 9732653 awarded by the National Science Foundation. The Government has certain rights in the invention. --

Signed and Sealed this

Twenty-fifth Day of May, 2004

A handwritten signature in black ink, reading "Jon W. Dudas". The signature is written in a cursive style with a large, looped initial "J".

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office



US006685956B2

(12) **United States Patent**
Chu et al.(10) **Patent No.:** **US 6,685,956 B2**
(45) **Date of Patent:** **Feb. 3, 2004**(54) **BIODEGRADABLE AND/OR
BIOABSORBABLE FIBROUS ARTICLES AND
METHODS FOR USING THE ARTICLES FOR
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University of New York, Stony Brook,
NY (US)**(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 88 days.(21) **Appl. No.:** **09/859,007**(22) **Filed:** **May 16, 2001**(65) **Prior Publication Data**

US 2002/0173213 A1 Nov. 21, 2002

(51) **Int. Cl.⁷** **A61F 2/02**(52) **U.S. Cl.** **424/423; 424/424; 424/425;**
424/426(58) **Field of Search** **424/423, 424,**
424/425, 426(56) **References Cited****U.S. PATENT DOCUMENTS**

3,975,565 A	8/1976	Kendall
4,043,331 A	8/1977	Martin et al.
4,323,525 A	4/1982	Bornat
4,345,414 A	8/1982	Bornat et al.
4,468,922 A	9/1984	McCrary et al.
4,689,186 A	8/1987	Bornat
4,810,180 A	3/1989	Isner
4,840,626 A	6/1989	Linsky et al.
4,878,908 A	11/1989	Martin et al.
4,911,867 A	3/1990	Burlet et al.
5,066,755 A	11/1991	Lemstra

5,296,172 A	3/1994	Davis et al.
5,480,436 A	1/1996	Bakker et al.
5,508,036 A	4/1996	Bakker et al.
5,569,528 A	10/1996	Van der Loo et al.
5,714,159 A	2/1998	Shalaby
5,783,111 A	7/1998	Ikkala et al.
5,795,584 A	8/1998	Totakura et al.
6,010,692 A	1/2000	Goldberg et al.
6,013,371 A	1/2000	Hager et al.
6,037,331 A	3/2000	Shalaby et al.
6,056,970 A	5/2000	Greenawalt et al.
6,060,582 A	5/2000	Hubbell et al.
6,090,910 A	7/2000	Shinoda et al.
6,106,913 A	8/2000	Scardino et al.
6,218,441 B1	4/2001	Meluch et al.

FOREIGN PATENT DOCUMENTS

WO	WO98/03267	1/1998
WO	WO01/26610 A1	4/2001
WO	WO01/27365 A1	4/2001

OTHER PUBLICATIONSDzenis et al., "Polymer Hybrid Nano/Micro Composites,"
*Proceedings of the American Society for Composites—Ninth
Technical Conference*, pp. 657–665 (1994).Bezwada et al., "Poly(p-Dioxanone) and Its Copolymers,"
Handbook of Biodegradable Polymers, # 29–61 (1997).*Primary Examiner*—Carlos Azpuru(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP(57) **ABSTRACT**

Biodegradable and/or bioabsorbable fibrous articles and methods for using the articles in medical applications are disclosed. The biodegradable and/or bioabsorbable fibrous articles, which are formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, comprise a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. Articles having specific medical uses include an adhesion-reducing barrier and a controlled delivery system. The methods include methods for reducing surgical adhesions, controlled delivery of a medicinal agent and providing controlled tissue healing.

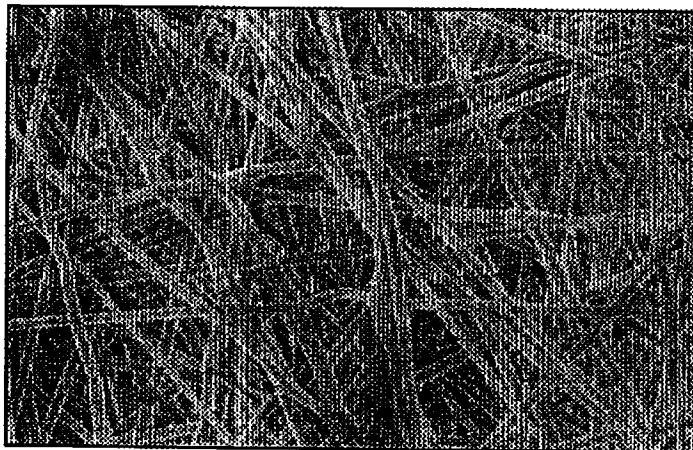
24 Claims, 14 Drawing Sheets

FIG. 1

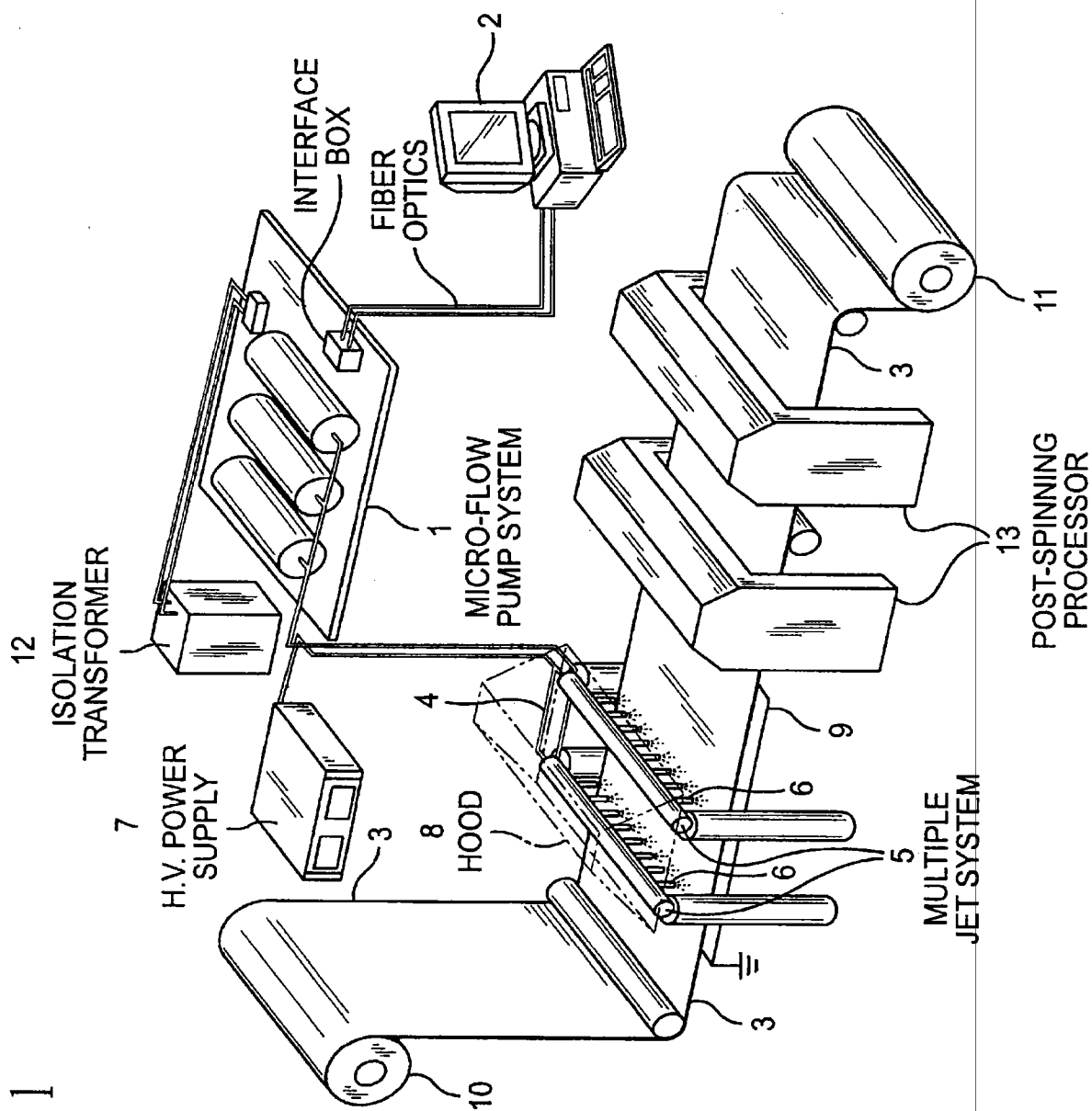
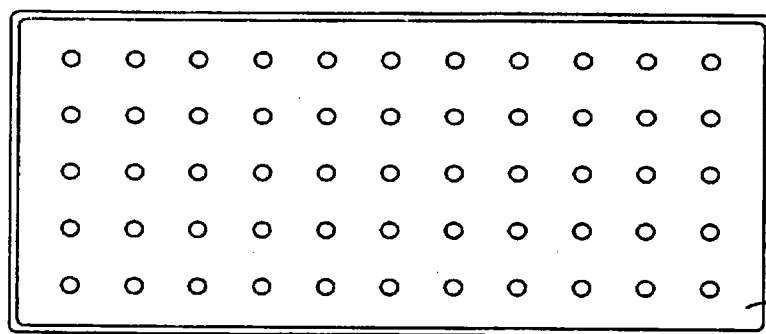


FIG. 2 (a)



FIG. 2C

FIG. 2 (b)



21

FIG. 2 (c)

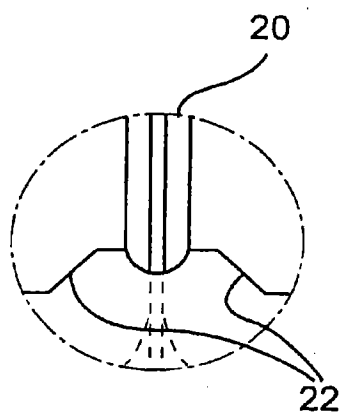


FIG. 3 (a)

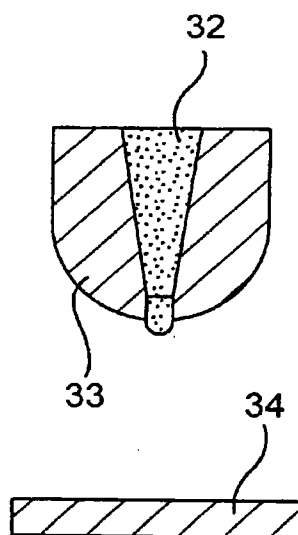


FIG. 3 (b)

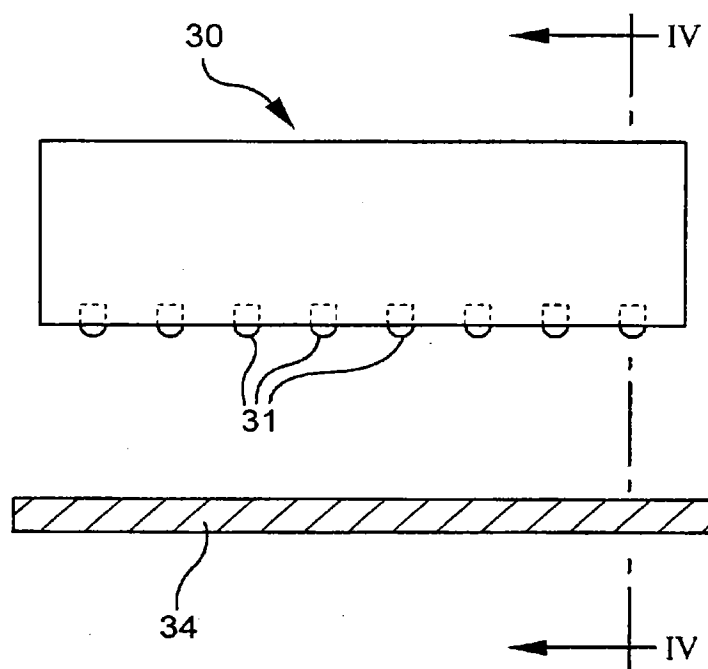


FIG. 3 (c)

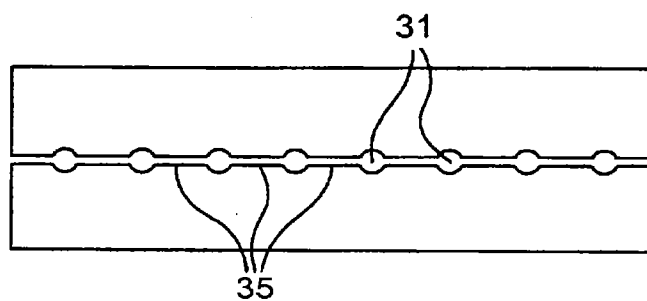


FIG. 4 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

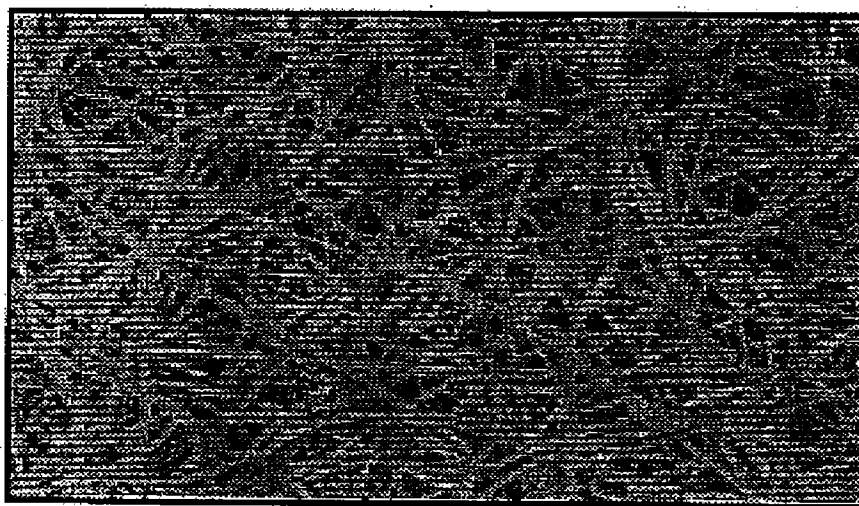


FIG. 5 SPUN MEMBRANE WITHOUT SALT

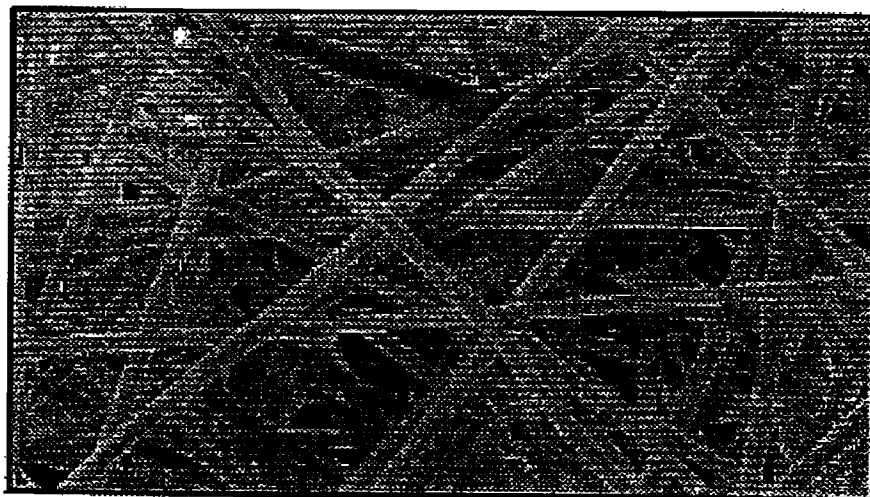


FIG. 6

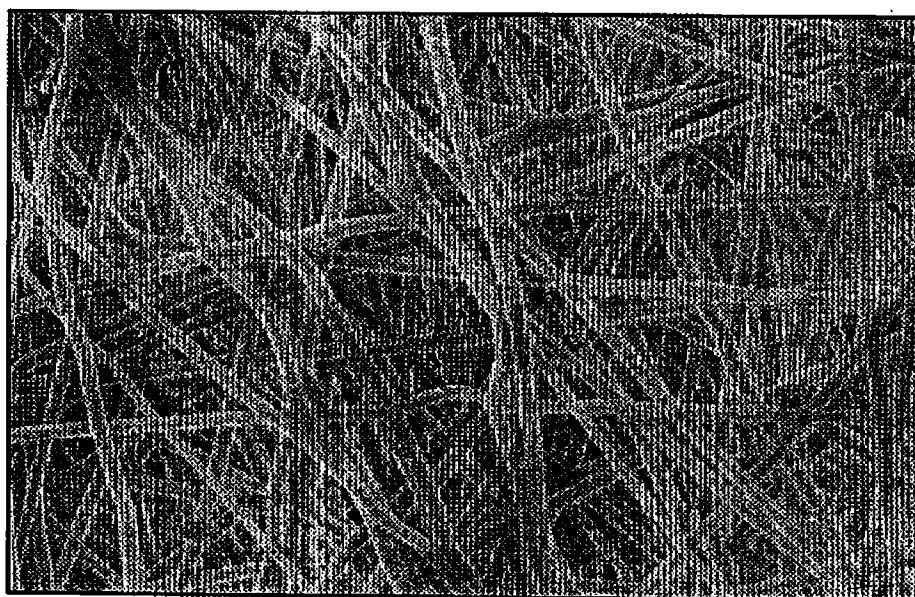


FIG. 7

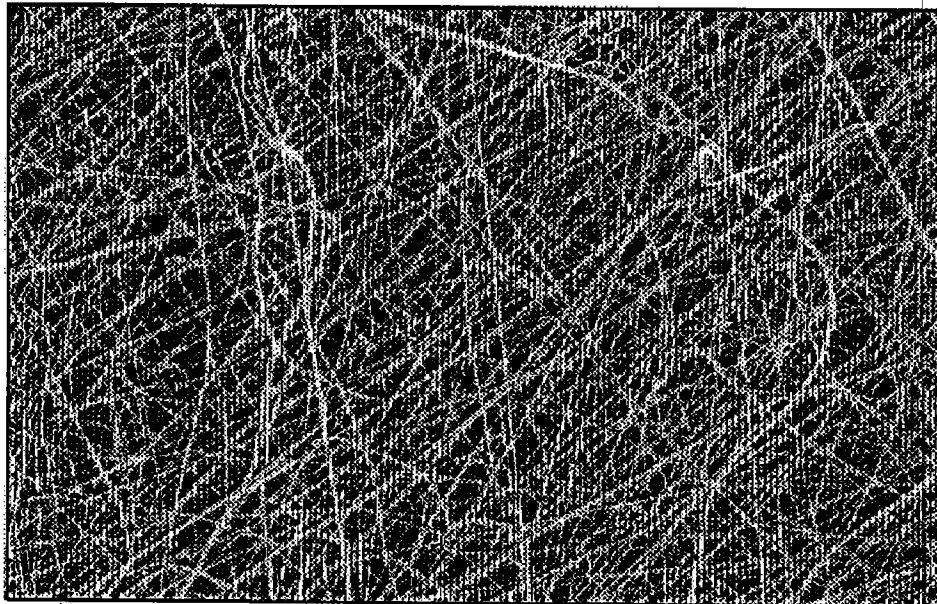


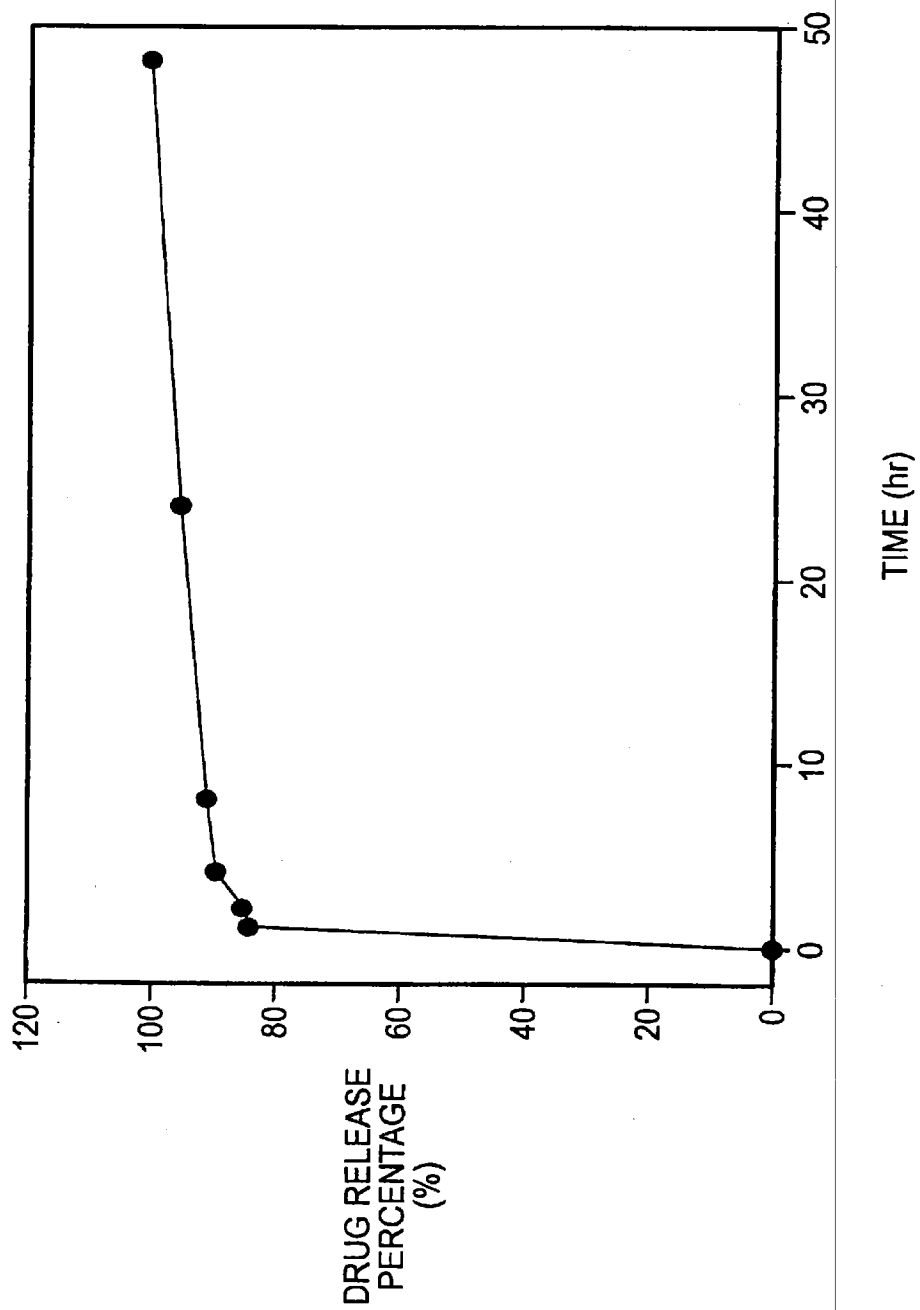
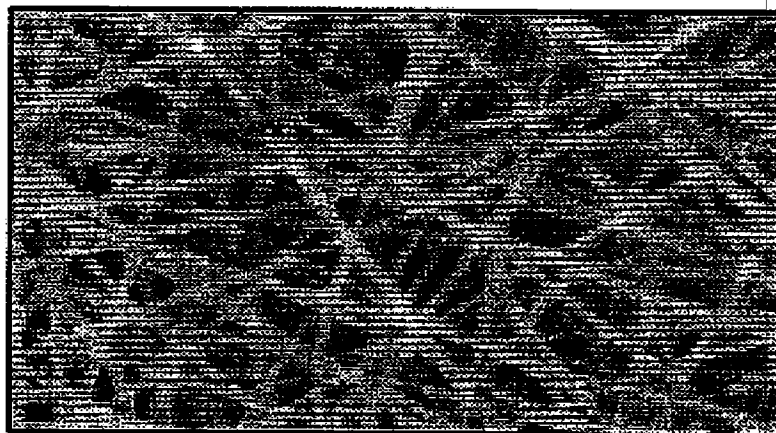
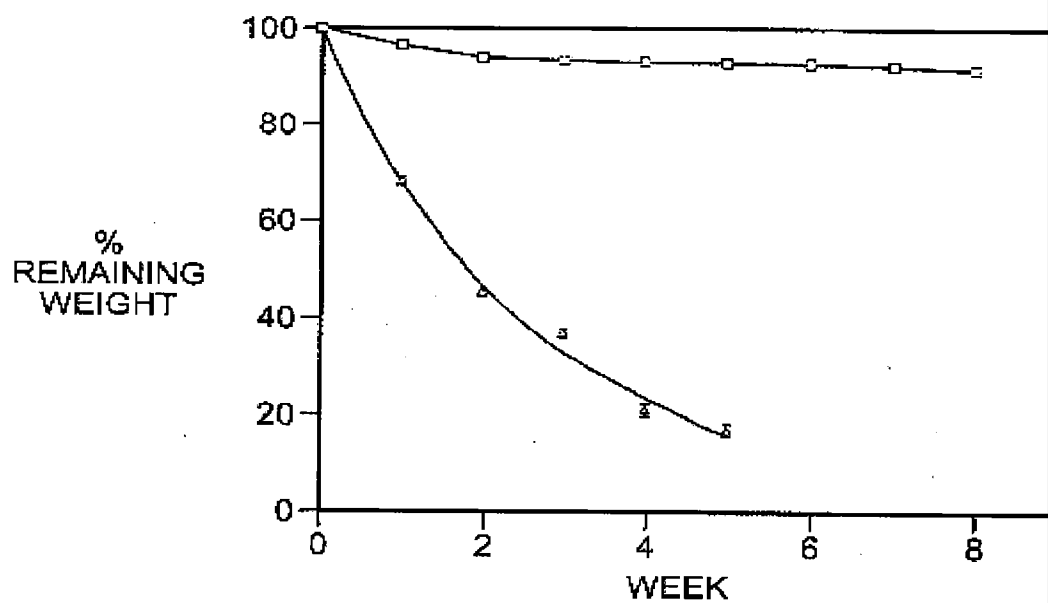
FIG. 8 IN VITRO DRUG RELEASE PROFILE

FIG. 9 SEM IMAGE OF ELECTROSPUN PLA MEMBRANEFIG. 10 BIODEGRADATION RATE OF ELECTROSPUN MEMBRANE

- △ AMORPHOUS PGA FILM
- P(DL)LA ELECTROSPUN FILM

FIG. 11 DUEL THICKNESS PLA MEMBRANE



FIG. 12 MEMBRANE AFTER 1 WEEK OF DEGRADATION



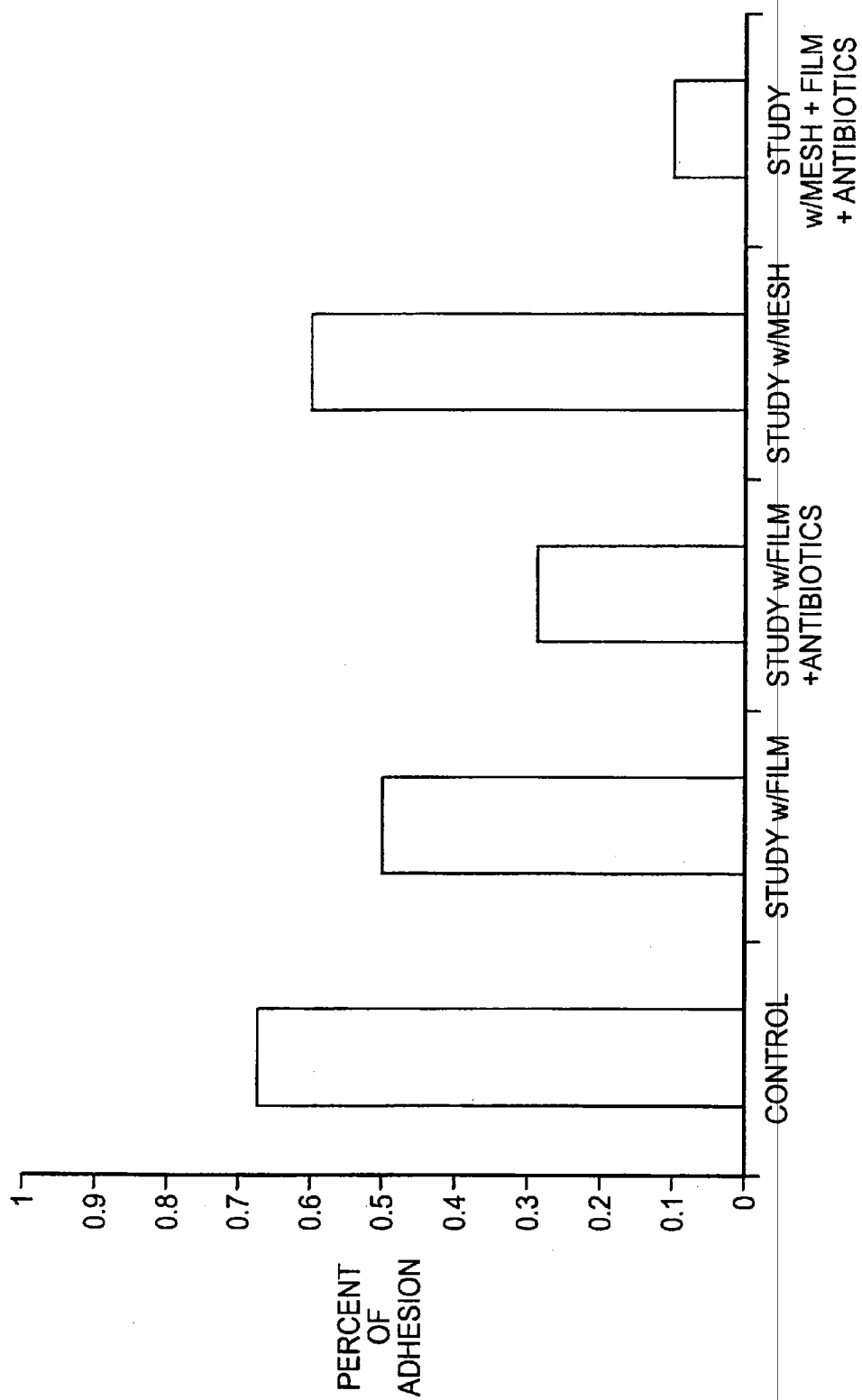
FIG. 13 INCIDENCE OF ADHESION

FIG. 14 CECAL ADHESION TENSION (N)

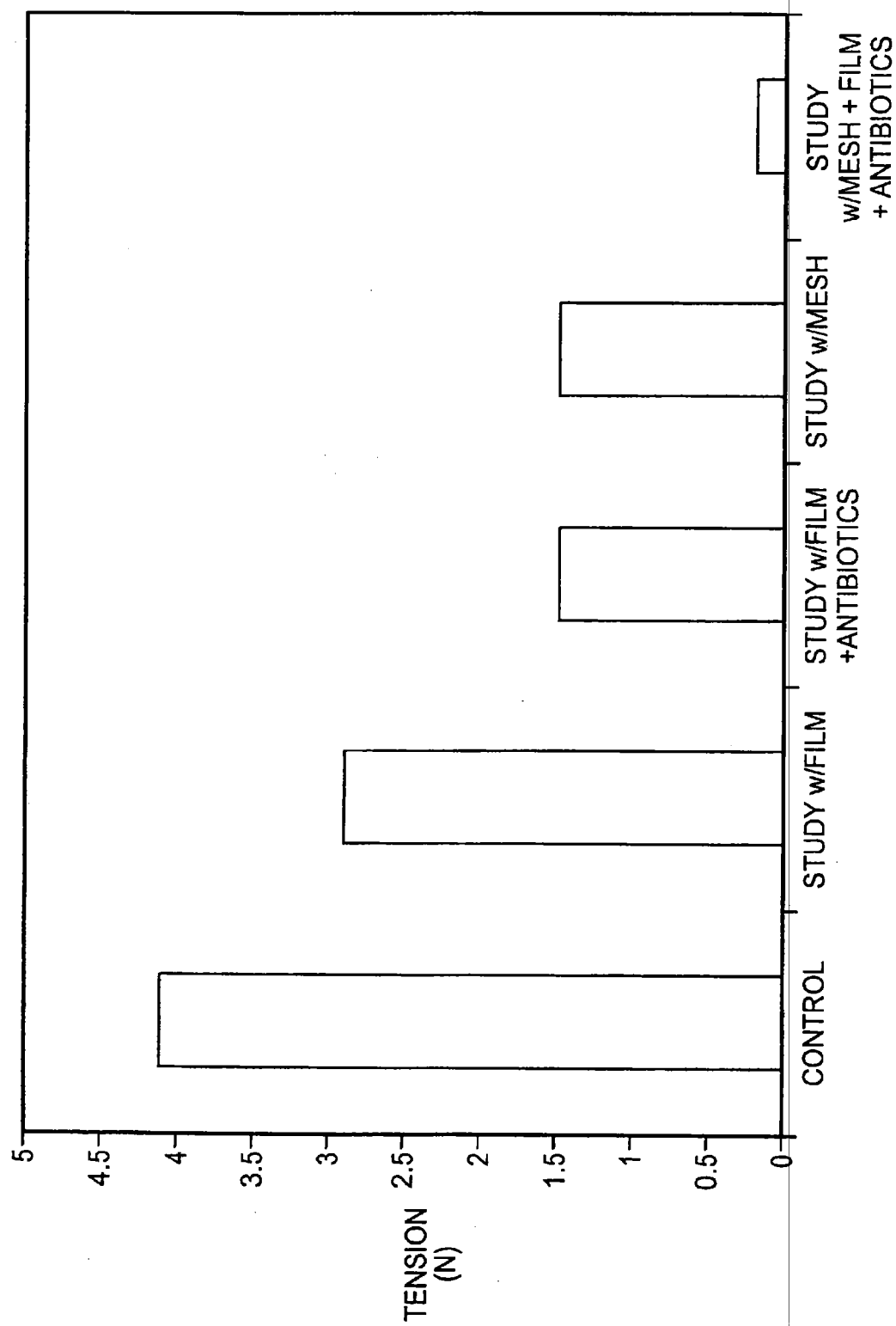


FIG. 15 ANTIBACTERIAL TEST RESULTS OF PLA MEMBRANE

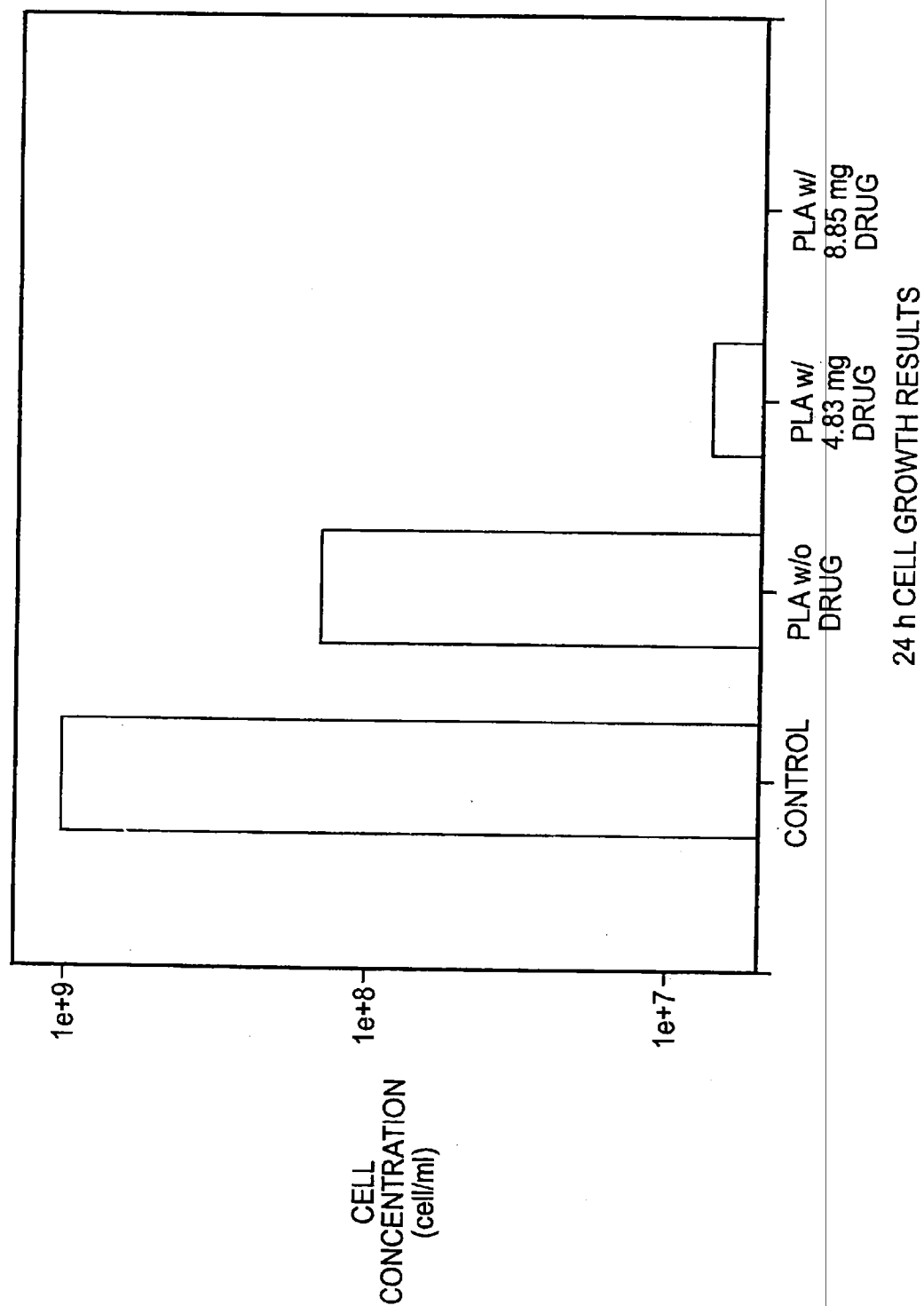


FIG. 16 SEM IMAGE OF AS-SPUN MEMBRANE

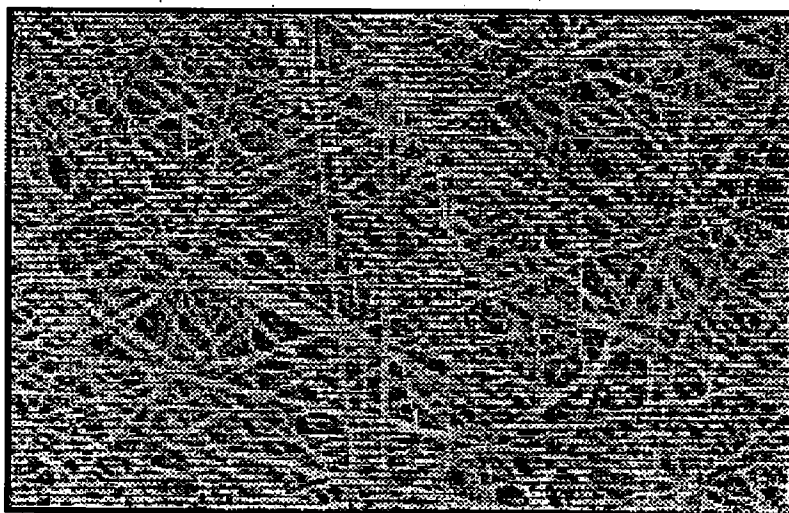
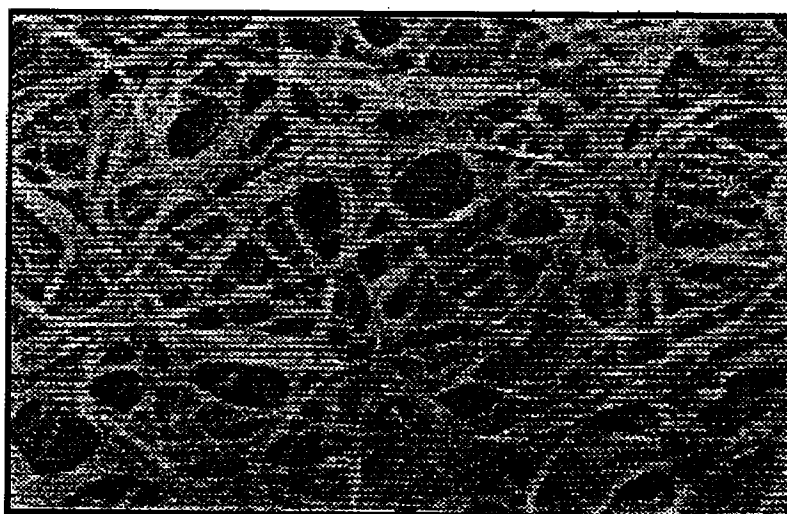


FIG. 17 IN-VIVO DEGRADATION AFTER A WEEK



BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fibrous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of

the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokine) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the

surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminoglycan can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

In one embodiment, the above described fibrous articles are in the form of a membrane.

The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

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In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the composite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegradation rate with utility in a controlled delivery system.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and

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examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic of an electrospinning system.

FIG. 2 is a schematic of an array of spinnerets for an electrospinning process.

FIG. 3(a) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. 3(b) is a cross-sectional view of the spinneret system of FIG. 3(a) as seen along viewing lines IV—IV thereof.

FIG. 3(c) is a bottom view of the multiple spinneret system of FIG. 3(a).

FIG. 4 is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4 .

FIG. 5 is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. 6 is an SEM of a membrane described in Example 1.

FIG. 7 is an SEM of a membrane described in Example 4.

FIG. 8 is a graph of the results of the drug release test described in Example 4.

FIG. 9 is an SEM of a PLA membrane described in Example 5.

FIG. 10 is a graph of the results of the biodegradation tests described in Example 6.

FIG. 11 is an SEM of the PLA membrane described in Example 7.

FIG. 12 is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. 13 is a graph of the results of the adhesion experiment described in Example 8.

FIG. 14 is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. 15 is a graph of the results of the antibacterial test described in Example 9.

FIG. 16 is an SEM of the as spun membrane described in Example 10.

FIG. 17 is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the

influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include polylactides, poly-glycolides, polycaprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000 nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorbable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorbable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between muscle tissue and bone; barriers between the esophagus and mediastinum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for

example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioabsorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsorbable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^5 . If the extrudate (conducting fluid) from each spinneret has a rate of about 10 $\mu\text{l}/\text{min}$, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tet-

rahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4 , K_2HPO_4 , KIO_3 , KCl, MgSO_4 , MgCl_2 , NaHCO_3 , CaCl_2 , or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. 1. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. 1, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system 1. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4 . Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system 1 is linked to a computer 2 which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane 3 and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system 1 feeds the conducting fluid to a multiple jet system 4 that contains manifolds 5 having a bank of spinnerets 6. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply 7. A hood 8 is positioned over the multiple jet system 4 to remove the solvent at a controlled evaporation rate.

A ground plate 9 is positioned below the multiple jet system 4 such that an electric field is created between the charged spinnerets 6 and the ground plate 9. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate 9, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support 3 is positioned between the charged spinnerets 6 and the ground plate 9 to collect the fibers which are formed from the spinnerets and to form an interconnected web of the fibers. The support 3 moves in the direction from the unwind roll 10 to the rewind roll 11.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer 12.

The post-spinning processors 13 have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the mem-

brane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed on even date herewith and incorporated herein for all purposes by reference.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magnetohydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2-3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused,

resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning.

In yet another method for producing membranes according to the present invention, reference will be made to FIG. 2. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets 20. The array of electrospinning spinnerets are assembled in a matrix 21 that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes 22. The spinneret 20 and the scanning electrodes 22 are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret 20 can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret 20 can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. 3(a)–3(c). In this apparatus, a multiple jet system 30 comprises an array of electrospinning spinnerets 31, each spinneret 31 being defined by a slit 32 formed in a slit-die 33 that is coupled to high voltage to serve as an electrode disposed above the ground plate 34. As shown in detail in FIG. 3(c), the spinnerets 31 are each interconnected by selectively narrow slits 35, such that each spinneret 31 is interconnected to a neighboring spinneret 31 by a slit 35. The conducting fluid will not flow through the slits 35, but will flow through each of the spinnerets 31 in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with con-

trolled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. 4) than the one with no salt added (FIG. 5). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl , KH_2PO_4 , KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated. Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The col-

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lecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. 6.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorbable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron

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Microscopy) image of the membrane containing the drug is shown in FIG. 7.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 nm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. 8.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. 9 shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm³, as compared to the neat resin (PLA) density of 1.3 g/cm³.

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. 10. A review of FIG. 10 reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 μ L/min to 70 μ L/min. An SEM of the resulting membrane is shown in FIG. 11.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared (FIG. 12). A comparison of FIGS. 11 and 12 reveals that this morphology results in a rapid weight loss in the first week. Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-

operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ -radiation doses from 5.15–25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylazine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A 1×1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned area (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibiotics (see FIG. 13). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. 14). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while 10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1×1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10).

All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesional strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0×7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. 15, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. 15 reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conducted using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug ratio of 9:1. A 20 kV positive voltage was applied to the electrode. An SEM of the initial as spun membrane (FIG. 16) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. 17.

A comparison of FIGS. 16 and 17 reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. An adhesion-reducing barrier comprising a biodegradable and/or bioabsorbable membrane, said membrane com-

prising a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

2. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different diameters.

3. An adhesion-reducing barrier according to claim 2, wherein said fibers of different diameters include fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

4. An adhesion-reducing barrier according to claim 2, wherein said membrane comprises at least about 20 weight percent of submicron diameter fibers.

5. An adhesion-reducing barrier according to claim 4, wherein said membrane comprises at least about 50 weight percent of submicron diameter fibers.

6. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

7. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

8. An adhesion-reducing barrier according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

9. An adhesion-reducing barrier according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

10. An adhesion-reducing barrier according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

11. An adhesion-reducing barrier according to claim 10, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

12. An adhesion-reducing barrier according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

13. An adhesion-reducing barrier according to claim 1, wherein said fibers have diameters in the range from about 10 up to 1,000 nanometers.

14. An adhesion-reducing barrier according to claim 13, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

15. An adhesion-reducing barrier according to claim 1, further comprising small blobs of biodegradable and/or bioabsorbable material.

16. An adhesion-reducing barrier according to claim 1, further comprising at least one medicinal agent.

17. An adhesion-reducing barrier according to claim 16, wherein said medicinal agent is contained within said fibers.

18. An adhesion-reducing barrier according to claim 17, further comprising fibers with different concentrations of said medicinal agent.

19. An adhesion-reducing barrier according to claim 17, further comprising fibers with different medicinal agents.

20. An adhesion-reducing barrier according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers.

21. An adhesion-reducing barrier according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

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22. An adhesion-reducing barrier according to claim 1, wherein said membrane has a controlled degradation rate.

23. An adhesion-reducing barrier according to claim 1, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

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24. An adhesion-reducing barrier according to claim 23, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,685,956 B2
DATED : February 3, 2004
INVENTOR(S) : Chu et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

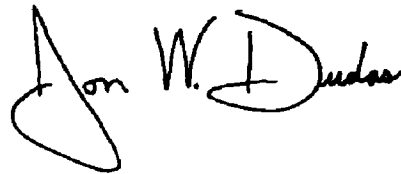
Column 1,

Line 5, after the title, insert:

-- "This invention was made with government support under Grant Nos. DMR 9984102 and DMR 9732653 awarded by the National Science Foundation. The Government has certain rights in the invention." --

Signed and Sealed this

Eighth Day of June, 2004

A handwritten signature in black ink, appearing to read "Jon W. Dudas", written over a horizontal line.

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office



US006713011B2

(12) **United States Patent**
Chu et al.

(10) **Patent No.:** **US 6,713,011 B2**
 (45) **Date of Patent:** **Mar. 30, 2004**

(54) **APPARATUS AND METHODS FOR
 ELECTROSPINNING POLYMERIC FIBERS
 AND MEMBRANES**

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Benjamin S. Hsiao, Setauket, NY (US);
Dufei Fang, Painted Post, NY (US)

(73) Assignee: **The Research Foundation at State
 University of New York, Stony Brook,
 NY (US)**

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 152 days.

(21) Appl. No.: **09/859,004**

(22) Filed: **May 16, 2001**

(65) **Prior Publication Data**

US 2002/0175449 A1 Nov. 28, 2002

(51) Int. Cl.⁷ **D01D 5/00; D01D 13/00;
 D06M 10/00**

(52) U.S. Cl. **264/465; 264/176.1; 425/135;
 425/145; 425/166; 425/174.8 E; 425/224;
 425/464**

(58) Field of Search **264/176.1, 465;
 425/135, 145, 166, 174.8 E, 224, 464**

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,975,565 A	8/1976	Kendall
4,043,331 A	8/1977	Martin et al.
4,323,525 A	4/1982	Bornat
4,345,414 A	8/1982	Bornat et al.
4,468,922 A	9/1984	McCready et al.
4,689,186 A	8/1987	Bornat
4,810,180 A	3/1989	Isner
4,878,908 A	11/1989	Martin et al.
4,911,867 A	3/1990	Burlet et al.
5,066,755 A	11/1991	Lemstra
5,296,172 A	3/1994	Davis et al.

5,569,528 A	10/1996	Van der Loo et al.
5,783,111 A	7/1998	Ikkala et al.
6,013,371 A	1/2000	Hager et al.
6,090,910 A	7/2000	Shinoda et al.
6,106,913 A	8/2000	Scardino et al.
6,218,441 B1	4/2001	Meluch et al.

FOREIGN PATENT DOCUMENTS

WO	WO98/03267 A1	1/1998
WO	WO01/26610 A1	4/2001
WO	WO01/27365 A1	4/2001

OTHER PUBLICATIONS

Bezwada et al., "Poly(p-Dioxanone) and Its Copolymers,"
Handbook of Biodegradable Polymers, # 29-61 (1997).
 Dzenis et al., "Polymer Hybrid Nano/Micro Composites,"
*Proceedings of the American Society for Composites-Ninth
 Technical Conference*, pp. 657-665 (1994).

Primary Examiner—Leo B. Tentoni

(74) Attorney, Agent, or Firm—Hoffmann & Baron, LLP

(57) **ABSTRACT**

An apparatus and method for electrospinning polymer fibers and membranes. The method includes electrospinning a polymer fiber from a conducting fluid in the presence of a first electric field established between a conducting fluid introduction device and a ground source and modifying the first electric field with a second electric field to form a jet stream of the conducting fluid. The method also includes electrically controlling the flow characteristics of the jet stream, forming a plurality of electrospinning jet streams and independently controlling the flow characteristics of at least one of the jet streams. The apparatus for electrospinning includes a conducting fluid introduction device containing a plurality of electrospinning spinnerets, a ground member positioned adjacent to the spinnerets, a support member disposed between the spinnerets and the ground member and movable to receive fibers formed from the conducting fluid, and a component for controlling the flow characteristics of conducting fluid from at least one spinneret independently from another spinneret.

50 Claims, 15 Drawing Sheets

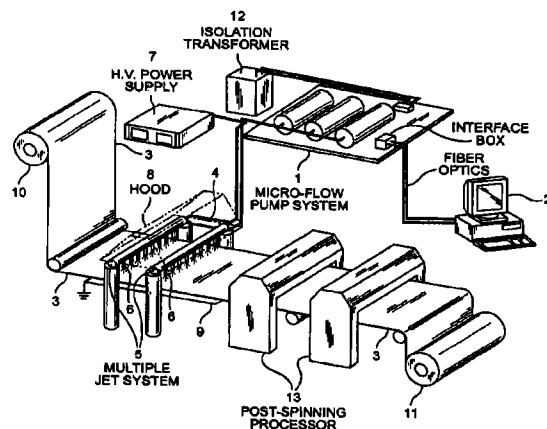


FIG. 1

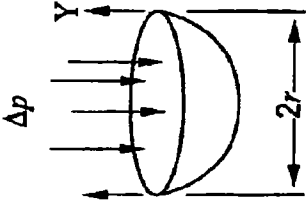


FIG. 2

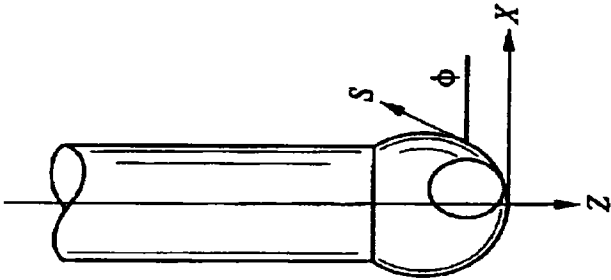


FIG. 3

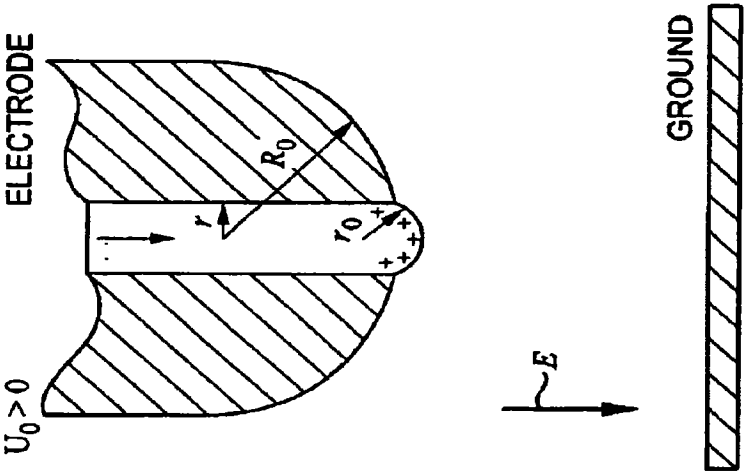


FIG. 4

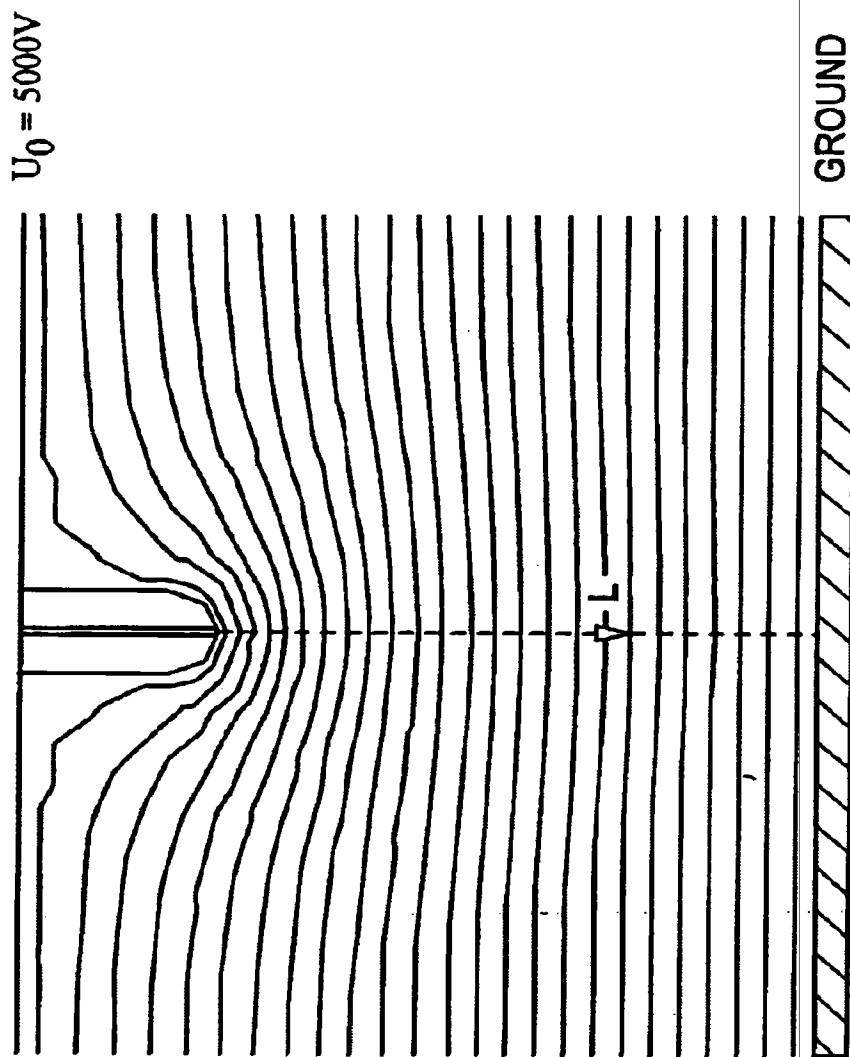


FIG. 5

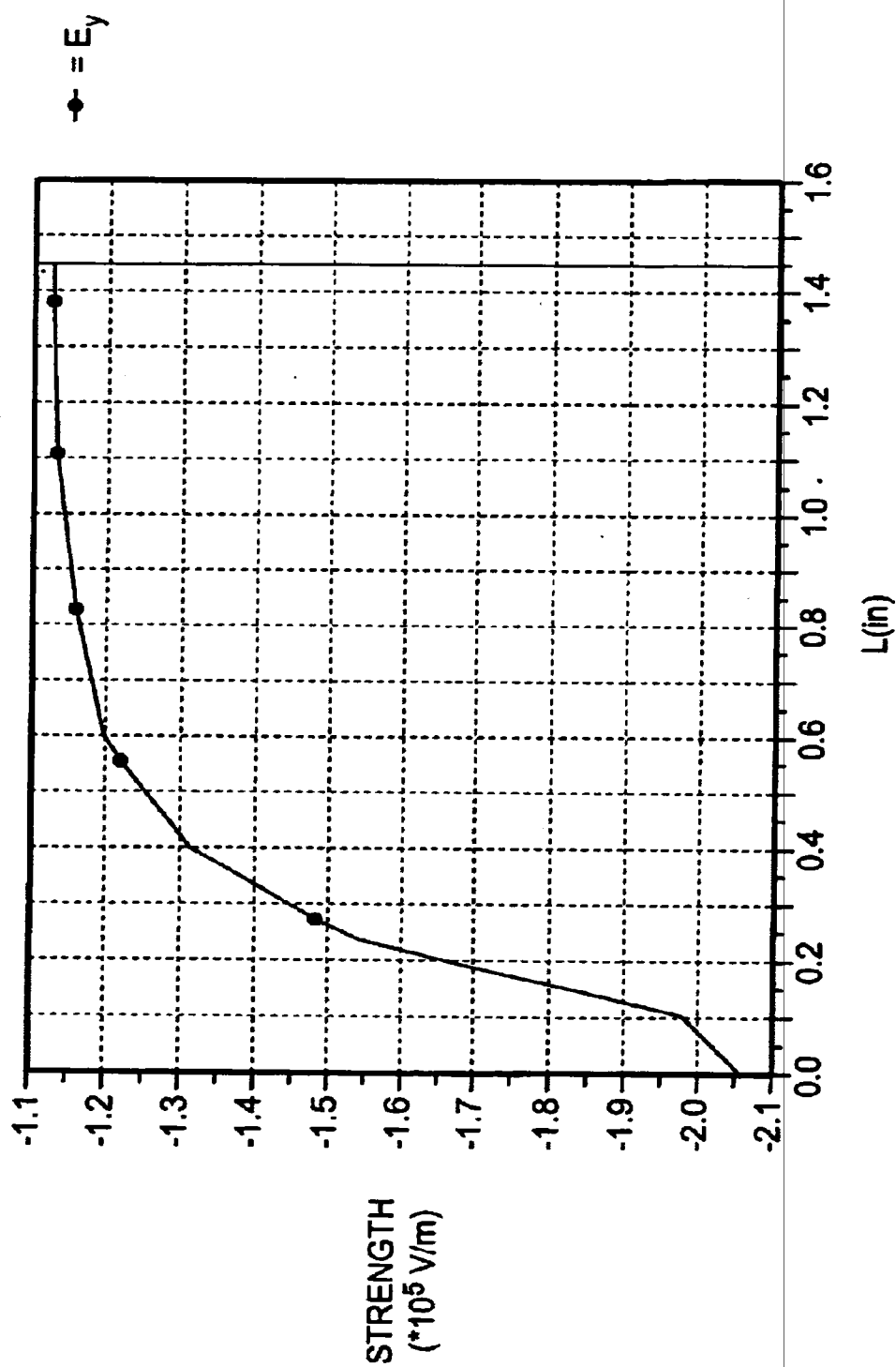


FIG. 6

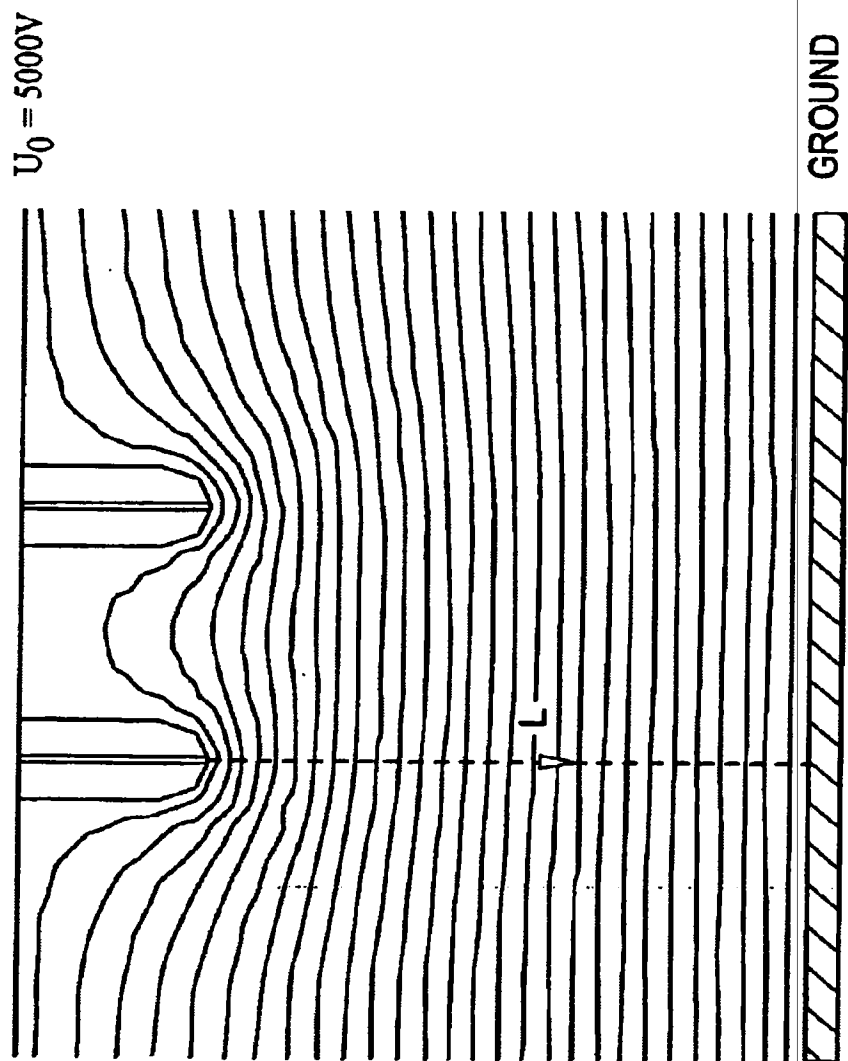
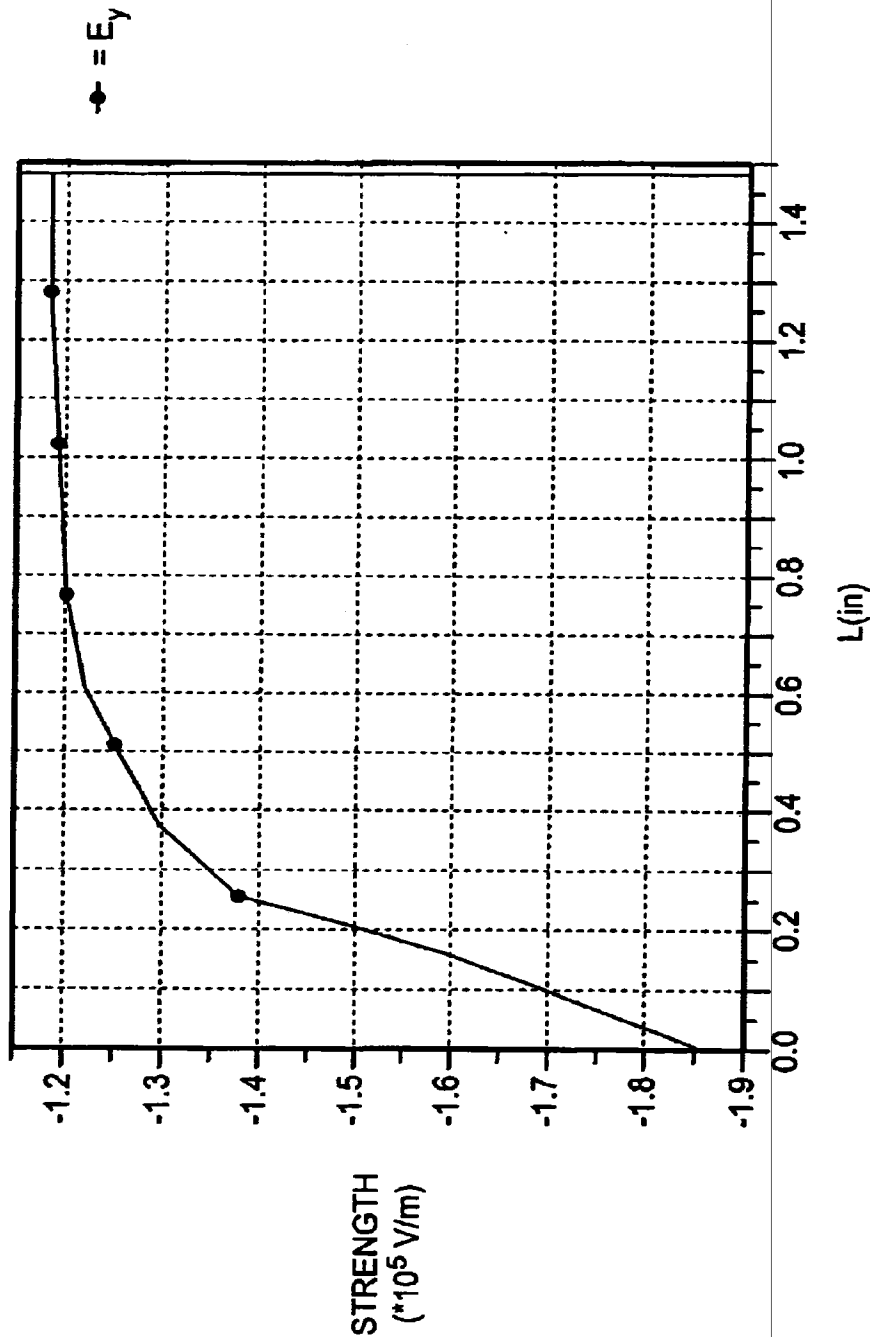


FIG. 7



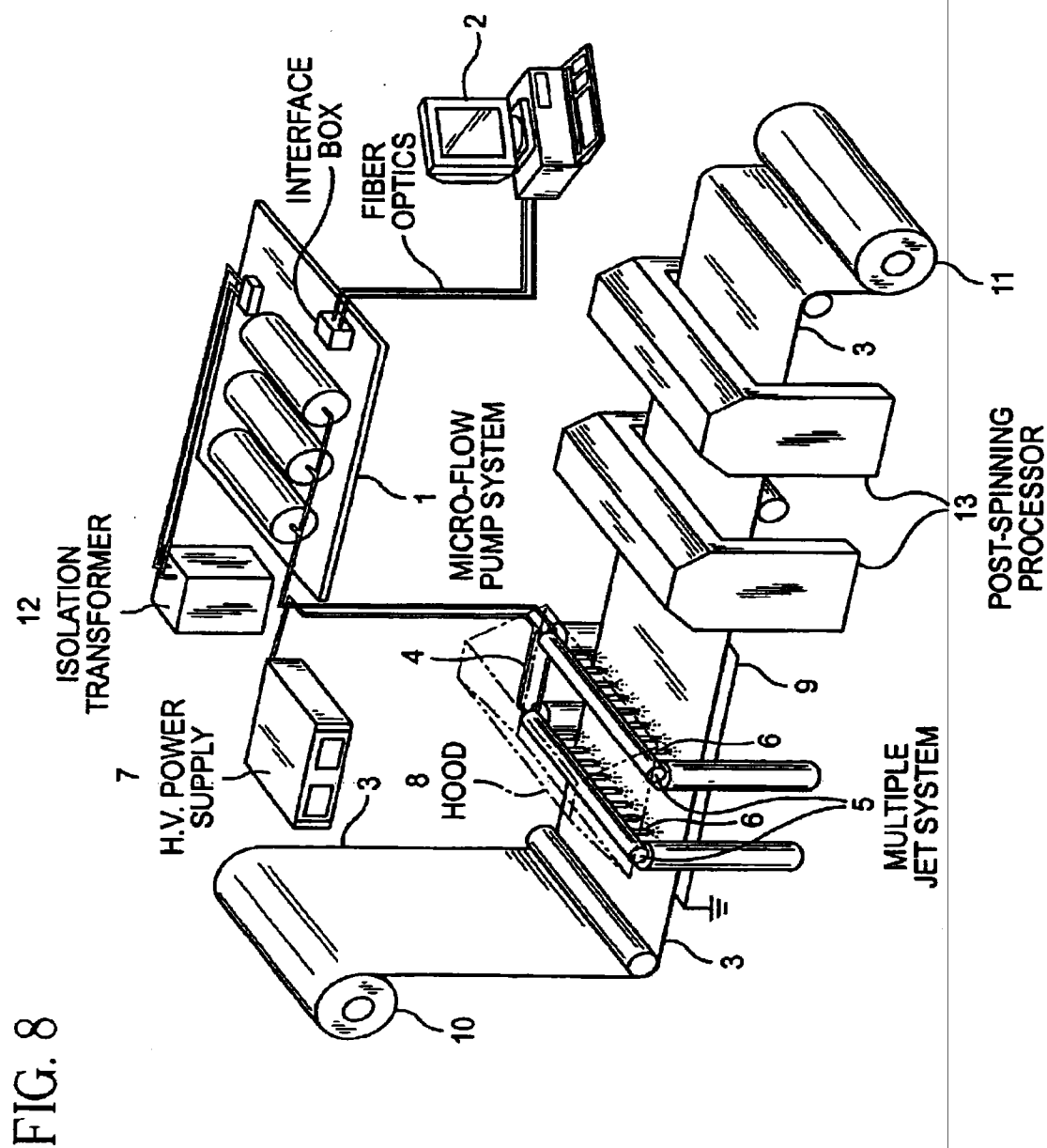


FIG. 9 (a)

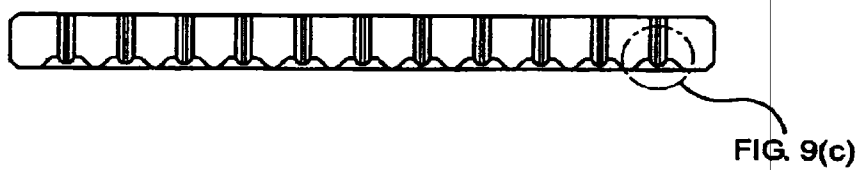


FIG. 9 (b)

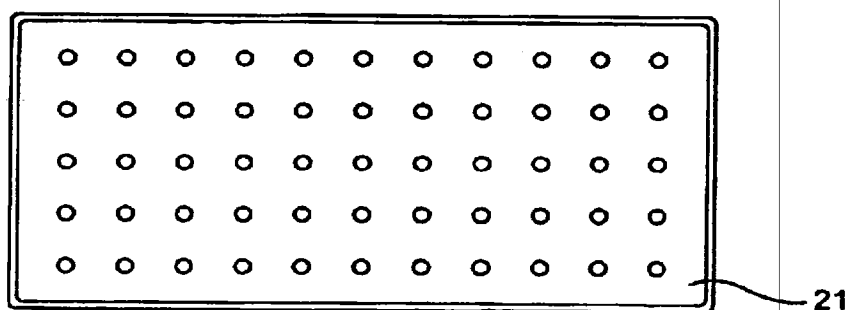


FIG. 9 (c)

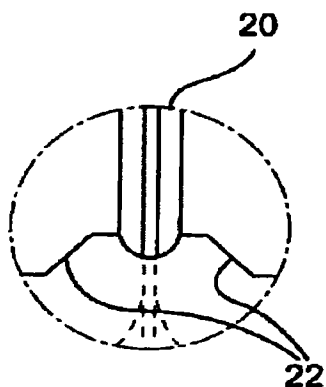


FIG. 10 (a)

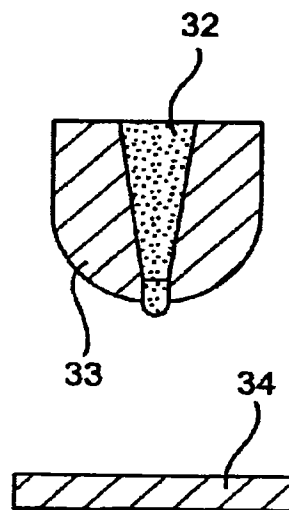


FIG. 10 (b)

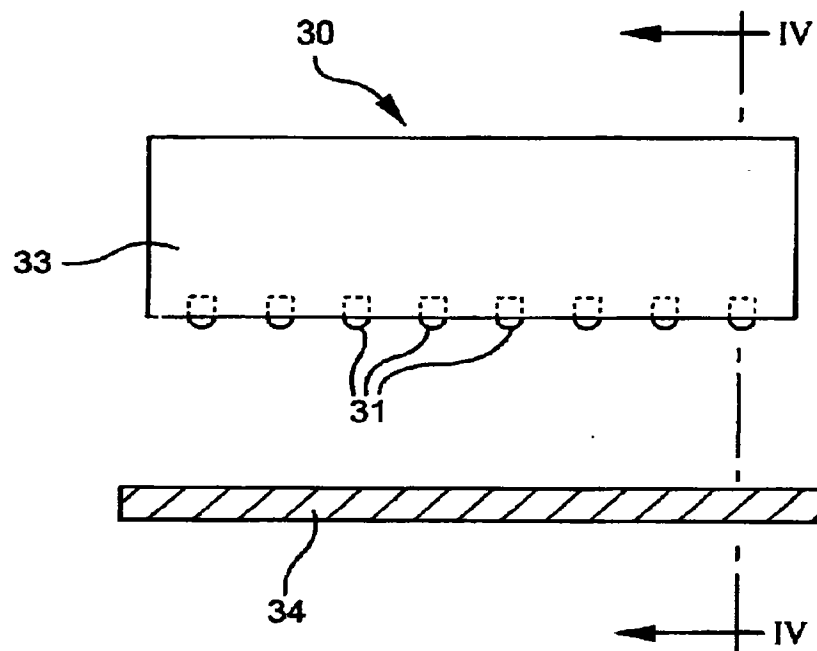


FIG. 10 (c)

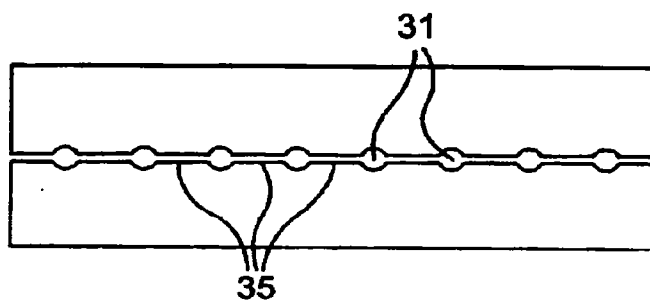


FIG. 11 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

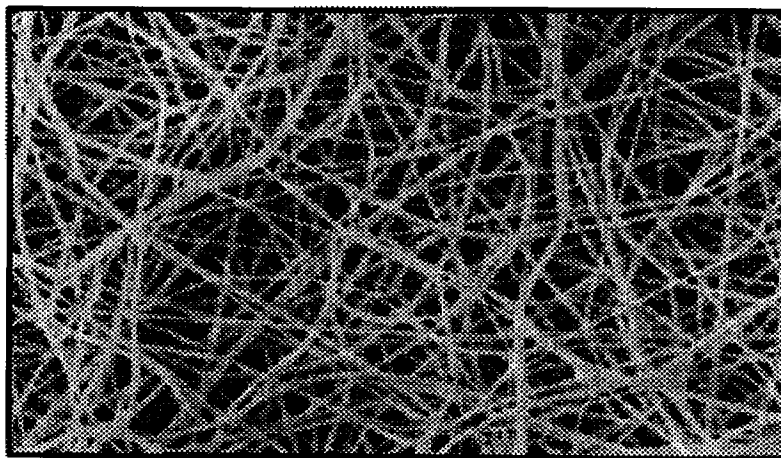


FIG. 12 SPUN MEMBRANE WITHOUT SALT

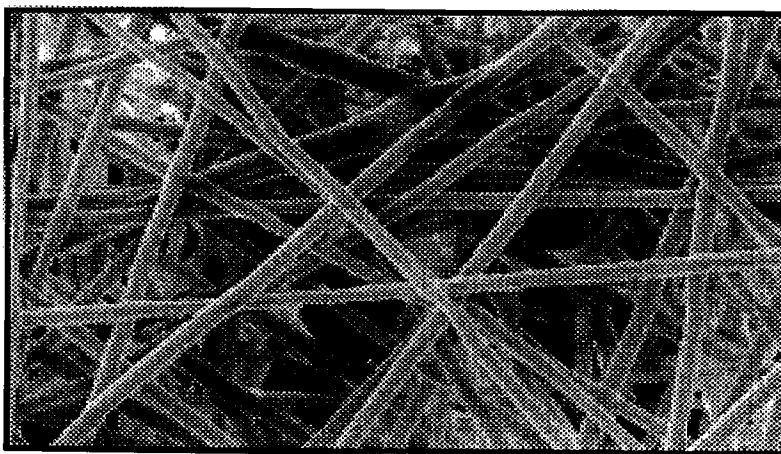


FIG. 13

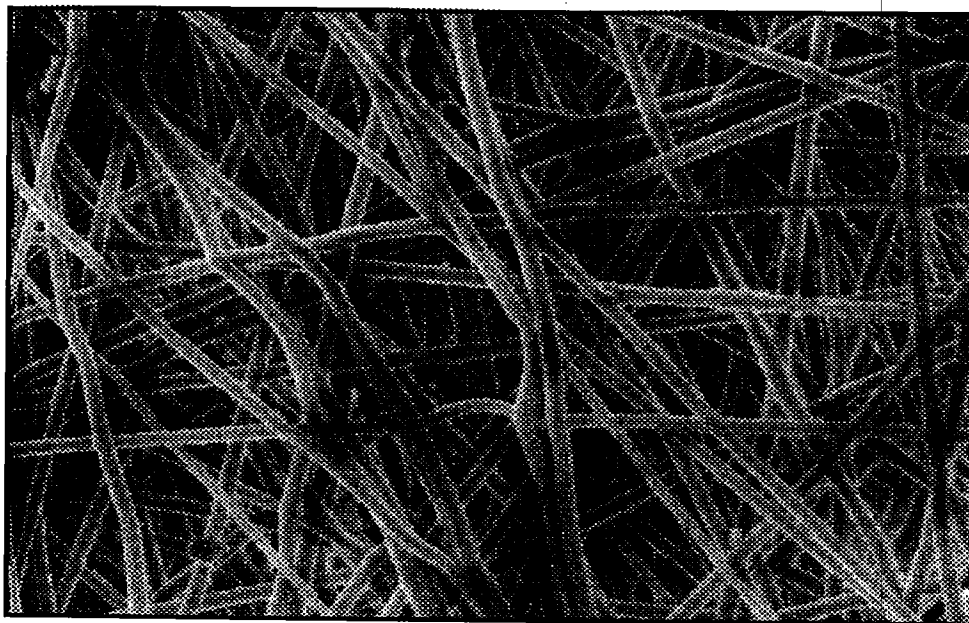


FIG. 14 SEM OF PAN MEMBRANE

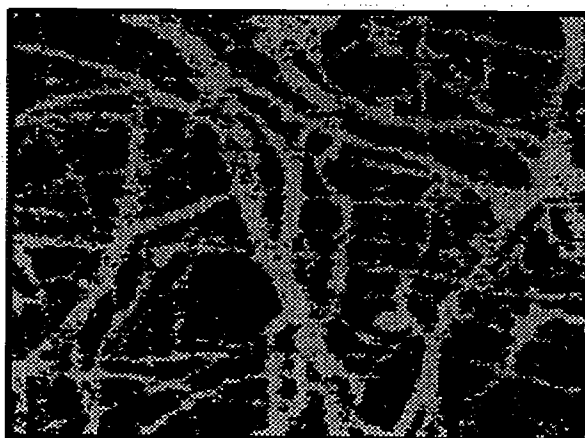


FIG. 15

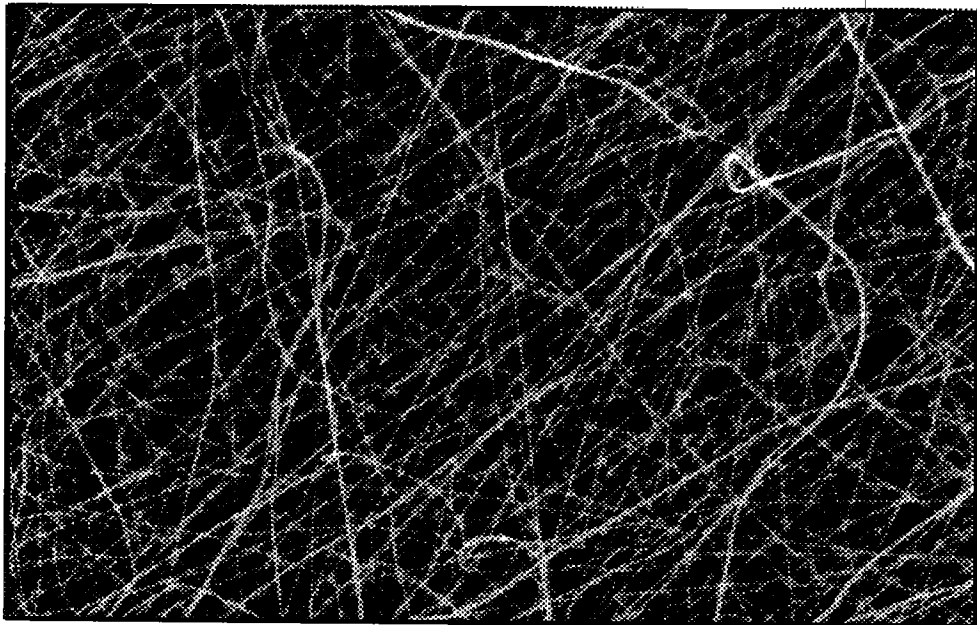


FIG. 16 SEM IMAGE OF ELECTROSPUN PLA MEMBRANE

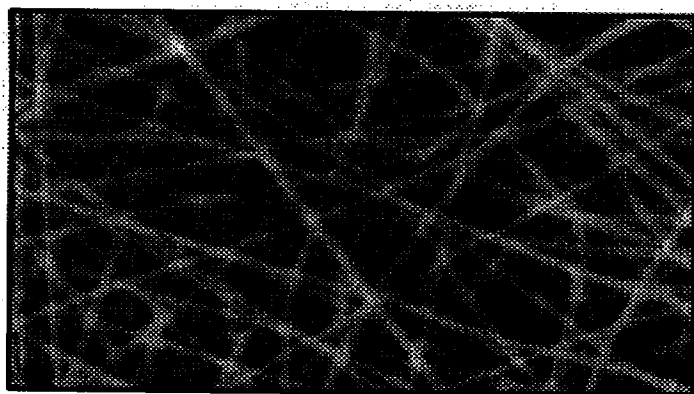


FIG. 17 DUEL THICKNESS PLA MEMBRANE

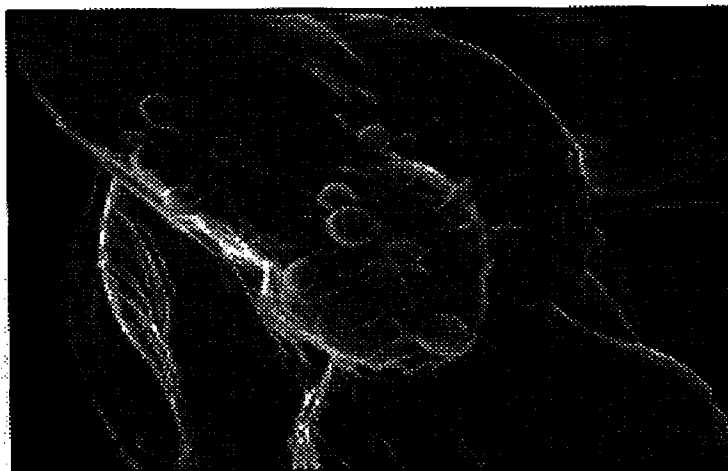
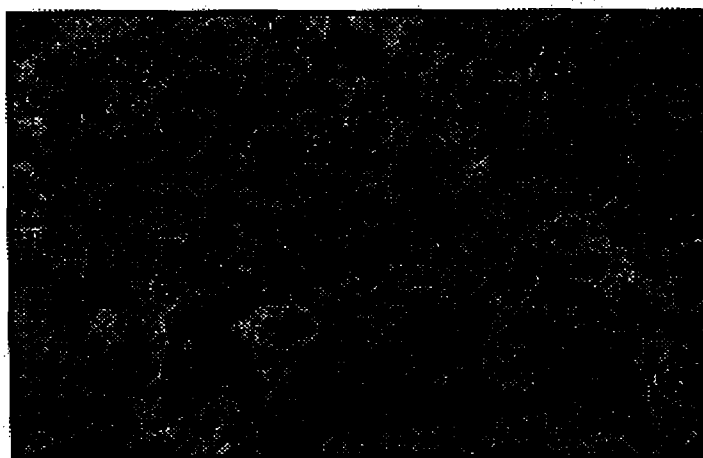


FIG. 18 SEM OF COPPER PLATED PAN MEMBRANE



APPARATUS AND METHODS FOR ELECTROSPINNING POLYMERIC FIBERS AND MEMBRANES

BACKGROUND OF INVENTION

The present invention relates to an apparatus and methods for electrospinning polymer fibers and membranes.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for electrospinning membranes containing a high percentage of small, e.g., nanosize, fibers. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fibrous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. For example, there is no teaching or suggestion of controlling jet formation, jet acceleration or fiber collection for individual jets. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

The above mentioned references do not address the problems associated with producing membranes or other articles on an industrial scale, without adversely affecting the performance characteristics of the resulting products.

Thus, there is a need for improved electrospinning methods for producing fibers and membranes on an industrial scale which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that polymeric fibers can be produced by an electrospinning process having improved control over fiber formation and transportation. In addition, membranes can be produced by electrospinning with the apparatus and according to the methods of the present invention on an industrial scale without the above-mentioned disadvantages.

In one aspect, the invention relates to a method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of a first electric field established between a conducting fluid introduction device and a ground source, which includes modifying the first electric field with a second electric field to form a jet stream of the conducting fluid. The conducting fluid introduction device is preferably a spinneret.

The second electric field can be established by imposing at least one field modifying electrode on the first electrostatic field. The field modifying electrode can be a plate electrode positioned between the conducting fluid introduction device and the ground source.

Preferably, the method includes feeding the conducting fluid to the conducting fluid introduction device at a controlled rate. The rate can be controlled by maintaining the conducting fluid at a constant pressure or constant flow rate.

In one embodiment, the method also involves controlling the electrical field strength at the spinneret tip by adjusting the electric charge on the field modifying electrode to provide a controlled diameter fiber.

In another embodiment, the method includes imposing a plurality of electrical field modifying electrodes to provide a controlled distribution of electrostatic potential between the spinneret and the ground source.

In another aspect, the invention relates to a method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of an electric field established between a spinneret and a ground source, which includes:

- a) forming an electrospinning jet stream of the conducting fluid; and
- b) electrically controlling the flow characteristics of the jet stream.

The flow characteristics of the jet stream can be electrically controlled by at least one electrode. The flow characteristics of the jet stream can also be electrically controlled by at least one pair of electrostatic quadrupole lenses. Preferably, the flow characteristics of the jet stream are electrically controlled by a plurality of pairs of electrostatic quadrupole lenses and, more preferably, by also using an alternating gradient technique.

In one embodiment, the method involves electrically controlling the flow characteristics of the jet stream to provide a controlled pattern over a desired target area. The controlled pattern can be provided by applying a waveform to the potential on at least one pair of electrostatic quadrupole lenses.

In yet another aspect, the invention relates to a method for forming a controlled-dimension and controlled-morphology membrane by electrospinning a plurality of polymer fibers from conducting fluid containing a polymer in the presence of an electric field established between a solution introduction device and a ground source, in which the method includes:

- a) forming a plurality of electrospinning jet streams of the conducting fluid; and

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b) independently controlling the flow characteristics of at least one of the jet streams.

Preferably, the flow characteristics of at least one of the jet streams are electrically controlled by at least one scanning electrode, more preferably, by at least one pair of scanning electrodes.

In one embodiment, the solution introduction device consists of a plurality of electrospinning spinnerets. Preferably, each spinneret produces an individual jet stream of the conducting fluid and, more preferably, the flow characteristics of each individual jet stream can be independently controlled.

Preferably, each spinneret has at least one scanning electrode for electrically controlling the flow characteristics of the individual jet stream. More preferably, each spinneret has two pairs of scanning electrodes for electrically controlling the flow characteristics of the individual jet stream.

It is contemplated that at least two spinnerets can deliver different solutions, wherein different solutions refers to different concentrations of polymer, different polymers, different polymer blends, different additives and/or different solvents.

In another aspect the invention is directed to an electrospinning apparatus for forming a membrane, which includes:

- a conducting fluid introduction device for providing a quantity of conducting fluid containing a polymer, the conducting fluid introduction device containing a plurality of electrospinning spinnerets for delivering the conducting fluid, the spinnerets being electrically charged at a first potential;

- a ground member positioned adjacent to the spinnerets and electrically charged at a second potential different from the first potential, thereby establishing an electric field between the spinnerets and the ground member;

- a support member disposed between the spinnerets and the ground member and movable to receive fibers formed from the conducting fluid; and

- means for controlling the flow characteristics of conducting fluid from at least one spinneret independently from the flow characteristics of conducting fluid from another spinneret.

Preferably, the means for independently controlling the flow characteristics includes at least one electrode disposed adjacent each spinneret, each electrode being charged at a potential different from and separate from the first potential.

Preferably, each spinneret has two pairs of scanning electrodes for electrically separately controlling the flow characteristics of conducting fluid from the spinneret.

The means for independently controlling the flow characteristics can include a means for individually electrically turning on and off a respective spinneret. Preferably, the means for individually electrically turning on and off a respective spinneret contains at least one scanning electrode associated with each spinneret.

The means for independently controlling the flow characteristics can also contain a means for applying an alternating gradient to the conducting fluid delivered from the spinnerets. Preferably, the means for applying said alternating gradient includes a plurality of pairs of electrostatic quadrupole lenses.

In one embodiment, the electrospinning apparatus includes a probe associated with at least one spinneret, the probe being disposed between the electrode and the ground member, the probe being electrically charged at a potential different from the spinneret and the electrode.

The electrospinning apparatus will preferably contain a pump for supplying conducting fluid to the conducting fluid

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introduction device at a predetermined pressure. The pump can also be adapted to control the supply rate of conductive fluid at a constant flow rate or at a constant pressure.

The electrospinning apparatus will preferably include a pump system for supplying different conducting fluids to at least two individual spinnerets.

In one embodiment, the conducting fluid introduction device contains a slit-die defining the plurality of spinnerets. The adjacent spinnerets can be interconnected by slits. In such an embodiment, the spinnerets can be defined by openings in the slit-die and the slits interconnecting the spinnerets are of configurations smaller than the openings. The apparatus can also contain a plurality of scanning electrodes disposed adjacent to each of the spinnerets.

In another embodiment, the solution introduction device includes a matrix defining the plurality of spinnerets, the spinnerets being disposed in the matrix in electrical isolation from each other. At least two individual spinnerets can be electrically charged to a different potential. The solution introduction device can also contain a plurality of individual electrodes in which at least one individual electrode is disposed adjacent to each individual spinneret. At least two individual electrodes can be electrically charged to a different potential.

In yet another aspect, the invention is directed to an apparatus for forming a membrane by electrospinning a plurality of polymer fibers from a conducting fluid which contains a polymer in the presence of an electric field between a conducting fluid introduction device and a ground source, in which the apparatus contains an improved conducting fluid introduction device which includes a plurality of spinnerets, each for independently delivering a controlled quantity of conducting fluid at a controlled pressure or flow rate, the spinnerets being charged at an electric potential and being disposed relative to each other to normally interfere with the electric field produced by adjacent spinnerets, each of the spinnerets having a tip at which conducting fluid exits configured to have an electrostatic field strength at each tip stronger than the liquid surface tension at each of the tips.

Each of the tips can be configured by having a tip with a selected geometric profile, a selected spatial relationship relative to other spinneret tips or a combination of both.

The apparatus containing the improved conducting fluid introduction device can also include an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets.

The apparatus containing the improved conducting fluid introduction device can also include a means for at least partially shielding a spinneret from electric field interference from adjacent spinnerets. The means for shielding can be a physical barrier disposed between adjacent spinnerets. The barrier will preferably have a conical shape.

The present invention provides an apparatus and methods for producing fibers and membranes by electrospinning with improved control over fiber formation and transportation. It also provides an apparatus and methods for producing membranes containing nanosize fibers on an industrial scale, without the above-mentioned disadvantages.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic of a fluid drop created from a capillary.

FIG. 2 is a schematic of a liquid drop suspended from a capillary.

FIG. 3 is a schematic of a droplet from a single spinneret in an electric field.

FIG. 4 is a schematic of the potential trajectory of a charged fluid jet from a single spinneret.

FIG. 5 is a graph of the electric field strength as a function of distance from the tip of a single spinneret.

FIG. 6 is a schematic of the potential trajectory of charged fluid jets from a multiple spinnerets.

FIG. 7 is a graph of the electric field strength as a function of distance from the tip of a spinneret in a multiple spinneret system.

FIG. 8 is a schematic of an electrospinning system.

FIG. 9 is a schematic of an array of spinnerets for an electrospinning process.

FIG. 10 (a) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. 10 (b) is a cross-sectional view of the spinneret system of FIG. 11 (a) as seen along viewing line IV—IV thereof.

FIG. 10 (c) is a bottom view of the multiple spinneret system FIG. 11 (a).

FIG. 11 is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4 .

FIG. 12 is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. 13 is an SEM of a membrane described in Example 1.

FIG. 14 is an SEM of a PAN membrane described in Example 2.

FIG. 15 is an SEM of a membrane described in Example 4.

FIG. 16 is an SEM of a PLA membrane described in Example 5.

FIG. 17 is an SEM of a dual thickness fiber PLA membrane described in Example 6.

FIG. 18 is an SEM of a copper plated PAN membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an apparatus and methods for producing polymeric fibers and membranes containing such fibers by electrospinning with improved control over fiber formation and transportation.

The present invention is also directed to an apparatus and methods for producing polymeric membranes by electrospinning a plurality of polymeric fibers simultaneously in a multiple jet system. This allows for high production rates and is necessary for a commercially viable process. However, in order to produce membranes by a multiple jet system, and maintain the desired performance characteristics of the membranes, it is necessary to control the flow characteristics of individual jet streams of the conducting fluid, as discussed more fully below.

By "flow characteristics" (of the conducting fluid) is meant the jet formation and jet acceleration of the conduct-

ing fluid which exits from the conducting fluid introduction device, e.g., the spinneret tip, as well as the directional flow of the jet stream in three dimensional space. Thus, controlling the flow characteristics can include controlling jet formation, controlling jet acceleration, directing the jet stream to a desired target in three dimensional space, steering the jet stream to different targets during the spinning process or a combination of these.

Nanofiber Fabrication Technique By Electrospinning

The invention is directed to improved methods and apparatus for electrospinning fibers and membranes from a conducting fluid containing a polymeric material.

The mechanical forces acting on the conducting fluid, which must be overcome by the interaction between an electrostatic field and the conducting fluid to create the electrospinning jet, can be understood by looking at a fluid drop in a capillary tube. For a fluid drop created from a capillary, as shown schematically in FIG. 1, a higher pressure is developed within the drop due to molecular interactions. This excess pressure Δp inside the drop, which acts upon the capillary cross-section area πr^2 , is counterbalanced by the surface tension Y acting on the circumference $2\pi r$, i.e. $\Delta p \cdot \pi r^2 = Y \cdot 2\pi r$, or

$$\Delta p = \frac{2Y}{r} \quad (1.1)$$

Formula 1.1 reveals that both the drop excess pressure Δp and the surface energy per unit drop volume $(4\pi^2 Y / (3)r^3) = 3Y/r$ become large when r is small.

The surface tension of a liquid drop hanging from a capillary tip (pendant drop), as shown schematically in FIG. 2, can be derived from the droplet shape, which is determined by a balance of all the forces acting upon the droplet, including gravity. The droplet surface tension can be related to the droplet shape as follows.

$$Y = g \Delta \rho r_0^2 / \beta \quad (1.2)$$

where $\Delta \rho$ is the density difference between fluids at the interface ($\Delta \rho = \rho$ for the droplet having a liquid/air interface), g is the gravitational constant, r_0 is the radius of drop curvature at the apex and β is the shape factor which can be defined by:

$$\begin{aligned} dx/ds &= \cos \phi \\ dz/ds &= \sin \phi \\ d\phi/ds &= 2 + \beta z - \sin \phi / x \end{aligned} \quad (1.3)$$

Numerical calculation can determine the value of β accurately.

A droplet from a single spinneret in an electrostatic field E , is shown schematically in FIG. 3. If a liquid has conductivity other than zero, the electric field will cause an initial current flow or charge rearrangement in the liquid. The positive charge will be accumulated at the surface until the net electric field in the liquid becomes zero. This condition is necessary for the current flow to be zero in the liquid. The duration τ of this flow is typically $\tau = \epsilon / \sigma$ where ϵ is the permittivity and σ is the conductivity of the liquid. With a surface charge density (per unit area) ρ_s , the (surface) force F_s exerted on the surface by the electrostatic field E on the droplet per unit area is:

$$F_s = \rho_s(\sigma)E \quad (1.4)$$

The conductivity σ of the liquid can be adjusted, e.g., by adding an ionic salt. Thus, the surface charge density per

unit area can be tuned accordingly. With a sufficiently strong electrostatic field at the tip, the surface tension Y can be overcome, i.e.,

$$F_s = \rho_s(\sigma)E \geq Y - \rho_0 Vg \quad (1.5)$$

with ρ_0 , V , and g being the density, the volume of the droplet and the gravitational acceleration, respectively. If this condition is met, the droplet shape will change at the tip to become the "Taylor" cone and a small jet of liquid will be emitted from the droplet. If the electrostatic field remains unchanged, the liquid moving away from the surface of the droplet will have net charges. This net excess charge is directly related to the liquid conductivity. Furthermore, the charged jet can be considered as a current flow, $J(\sigma, E)$, which will, in turn, affect the electric field distribution on the tip of the droplet, i.e.,

$$E = E_0 + E'(J) \quad (1.6)$$

with E_0 being the applied field threshold in the absence of fluid flow. For polymer solutions above the overlap concentration, the evenly distributed charges in the jet repel each other while in flight to the target (ground). Thus the polymer chains are continuously being "stretched" in flight until the stretch force is balanced by the chain restoring force or the chains are landed on the target, whichever comes first.

In the electrospinning process according to the invention, a key requirement is to maintain the droplet shape. This requirement involves control of many parameters including liquid flow rate, electric and mechanical properties of the liquid, and the electrostatic field strength at the tip. In order to achieve high field strengths, the curvature of the electrode at the tip has to be sharp (small radius R_0). However, since a stable pendant droplet is controlled by the shape factor β , the curvature r_0 and thus R_0 could not be too small. FIG. 4 shows, as an example, estimates of equal potential lines of a single electrode configuration with a set of specific geometric parameters and the force line for a charge particle in the trajectory that is normal to the equal potential lines. FIG. 5 shows the estimated electric field strength along the jet direction from the tip of the electrode to the ground (plate).

Sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6 . If the extrudate (conducting fluid) has a rate of about 20 $\mu\text{l}/\text{min}$, the final filament speed will be about 136 m/s, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds. For example, if a single jet is capable of processing a 40 wt % polymer solution at a rate of 20 $\mu\text{l}/\text{min}$ (i.e. 8 mg/min), then a production unit of 100 jets can produce about 500 g of a membrane in 12 hours of operation. As the average membrane density is about 0.25 g/cm³ and the average membrane thickness is about 25 microns, about 160 sheets of a membrane (with dimensions of 20x25 cm²) can be produced per day.

The conducting fluid will preferably include a solution of the polymer materials described more fully below. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. Typical solvents include a solvent selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), methylene chloride, dioxane, ethanol, chloroform, water or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH₂PO₄, K₂HPO₄, KIO₃, KCl, MgSO₄, MgCl₂, NaHCO₃, CaCl₂ or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to the spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

Preferably the electrospinning process includes multiple jets. This allows for the production of membranes containing small diameter fibers in very high yield, making it useful for production on an industrial scale. However, there are constraints associated with trying to use multiple jets in an electrospinning process.

For a configuration with multiple jets, two main factors are to be considered: 1) the liquids should be delivered, either at constant pressure or constant flow rate, to each separate spinneret; and 2) the electrostatic field strength at each tip of the electrode should be strong enough to overcome the liquid surface tension at that tip. The first factor has been resolved by careful mechanical design for controlled solution distribution to each of the spinnerets. With electrodes being placed close to one another, the electrostatic field distribution is changed and the field strength at tip is normally weakened because of the interference from nearby electrodes, i.e.,

$$E_i = E_i^0 + \sum_{j \neq i} E_{ij} + \sum_j E'_{ij}(J_j) \quad (1.7)$$

where E_i^0 is the unperturbed electric field strength due to the single electrode i . E_{ij} is the electric field at location i contributed by electrode j , and $E'_{ij}(J_j)$ is the interference electric field caused by the current J of jet j . FIG. 6 shows the equal potential line of a double jet configuration with the electrodes having the geometrical parameters as that of a single jet.

By following Equation (1.5) for a single jet, the criteria for the multiple jet operation are that, in addition to Equation (1.7), each jet (i) has to meet the following condition:

$$\rho_s(\sigma_i)E_i \geq Y - \rho_0 Vg \quad (1.8)$$

Both conditions for Equations (1.7) and (1.8) should be met for multiple jet operation. The multiple jet apparatus of the present invention was based on these two criteria. For example, FIG. 7 shows the estimated electric field strength along the direction from the tip to the ground. In comparison with FIG. 5, the field strength is less in absolute value. A separate calculation could show that in order to achieve the same field strength as the original unperturbed single jet, the electric potential has to increase from 5.0 kV to 5.6 kV. This demonstrates that the electric field strength for multiple jets can be calculated by using Equation (1.7). Furthermore, a shielding system or a specially shaped electrode to produce a different electric potential may be used to partially screen out the interference from nearby electrodes, making the

scale up operation practical. Numerical estimates, including jet effects based on Equation (1.7), can be used to guide and to obtain an optimal design for specific operations.

With multiple jets, as the electrodes are placed close to one another, the electrostatic field distribution is changed and the field strength of the spinneret *i* at the tip is altered by the presence of nearby electrodes. The net field strength at the tip *i* can be represented by three combinations: (1) the unperturbed electric field strength due to the single electrode *i*, (2) the sum of the electric field strength at location *i* due to all other electrodes, and (3) the electric field strength at location *i* generated by all jets (including *i*). This net field strength at tip *i* (E_i) can then be used to set the criteria for electrospinning, i.e., the product of surface charge density of the conducting fluid at tip *i* (S_i) times E_i together with the gravity effect should overcome the surface tension of the field at tip *i*. These rules represent the fundamental criteria for efficient multiple jet operation and permit optimal design for specific operations that involve multiple parameter adjustments.

In accordance with the present invention, different approaches have been developed to provide for efficient multiple jet operation. These approaches include improvements in the multiple jet electrospinning apparatus to provide sufficient field strength to overcome the surface tension of the conducting fluid and the electric field interference from adjacent spinnerets and jet streams. For example, a spinneret tip configuration can be provided to allow for efficient multiple jet spinning. The spinneret tip configuration can include a selected geometric profile to provide a controlled charge distribution in the conducting fluid at the spinneret tip as discussed above. The spinneret tip configuration can also include a selected spatial relationship for the spinneret tips relative to each other. For example, the distance from individual spinneret tips to the ground source can be varied, depending upon the relative distance between adjacent spinnerets, to provide more efficient multiple jet spinning.

Another example of an improved electrospinning apparatus is to provide an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets. Another example includes providing a means for at least partially shielding the electric field interference, such as a physical barrier disposed between adjacent spinnerets.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. 8. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. 8, the conducting fluid, which contains the polymer, is supplied by a micro-flow pump system 1. The conducting fluid preferably contains a polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4 . The pump system 1 is linked to a computer 2 which controls the flow rate of the conducting fluid by controlling pressure or flow rate. Optionally, different flow rates can be provided and controlled to selected spinnerets. The flow rate will change depending upon the speed of the support membrane 3 and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system 1 feeds the conducting fluid to a multiple jet system 4 that contains manifolds 5 having a bank of spinnerets 6. The spinnerets each have a tip geometry which allows for stable jet formation and transportation,

without interference from adjacent spinnerets or jet streams. A charge in the range of about 20 to about 50 kV is applied to the spinnerets by a high voltage power supply 7. A hood 8 is positioned over the multiple jet system 4 to remove the solvent at a controlled evaporation rate.

A ground plate 9 is positioned below the multiple jet system 4 such that an electric field is created between the charged spinnerets 6 and the ground plate 9. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate 9, forming small, e.g. sub-micron, diameter filaments or fibers.

A moving support membrane 3 is positioned between the charged spinnerets 6 and the ground plate 9 to collect the fibers which are formed from the spinnerets and to form an interconnected web of the fibers. The support membrane 3 moves in the direction from the unwind roll 10 to the rewind roll 11.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer 12.

The post-spinning processors 13 have the functions of drying, annealing, membrane transfer (for example, from a stainless mesh substrate to another substrate, e.g., a Malox mesh) and post-conditioning.

Post-conditioning can include additional processing steps to change the physical characteristics of the membrane itself, e.g., post-curing, or to modify the membrane by incorporating other materials to change the properties of the resulting membrane, e.g., solution coating, spin casting or metal/metal oxide plating the membrane.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. Additional embodiments or modifications to the electrospinning process and apparatus are described below.

Variation of Electric/mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magneto-hydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be alleviated.

Electrode Design

In another embodiment for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, as discussed above, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let

the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of the spinneret, the jet formation can be controlled and adjusted. Such an electrode configuration should greatly reduce the required applied potential on the spinneret from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another preferred embodiment for producing membranes according to the present invention, the jet stream flight is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (or composite electrode), i.e., the probe electrode and the plate electrodes, can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area. The composite electrode can also be utilized to manipulate the jet stream. By changing the electrostatic potential, the jet stream acceleration is altered, resulting in varying the diameter of the formed nano-fiber. This electrostatic potential variation changes the jet stream stability, and therefore, corresponding changes in the composite electrode can be used to stabilize the new jet stream. Such a procedure can be used to fine-tune and to change the fiber diameter during the electrospinning process.

Jet Manipulation

In yet another embodiment, the jet stream can be focused by using an "Alternating Gradient" (AG) technique, widely used in the accelerator technology of high-energy physics. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the yz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another embodiment for producing membranes according to the present invention, reference will be made to

FIG. 9. In this embodiment, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets 20. The array of electrospinning spinnerets are assembled in a matrix 21 that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes 22. The spinneret 20 and the scanning electrodes 22 are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret 20 can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret 20 can deliver a different solution, e.g., each containing a different drug or concentration. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In yet a further embodiment for producing membranes in accordance with the present invention, reference is made to FIGS. 10(a)–10(c). In this embodiment, a multiple jet system 30 comprises an array of electrospinning spinnerets 31, each spinneret 31 being defined by a slit 32 formed in a slit-die 33 that is coupled to high voltage to serve as an electrode disposed above the ground plate 34. As shown in detail in FIG. 10(c), the spinnerets 31 are each interconnected by selectively narrow slits 35, such that each spinneret 31 is interconnected to a neighboring spinneret 31 by a slit 35. The conducting fluid will not flow through the slits 35, but will flow through each of the spinnerets 31 in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. First, the slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. Second, the presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. Third, the presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. 11) than the one with no salt added (FIG. 12). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl , KH_2PO_4 , KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

The apparatus and methods according to the invention can be used for electrospinning any fiberizable material.

Examples of such materials include polymers, such as PLA, PGA, PEO, nylon, polyesters, polyamides, poly(amic acids), polyimides, polyethers, polyketones, polyurethanes, polycaprolactones, polyacrylonitriles and polyaramides.

The fiberizable material is preferably a biodegradable or bioabsorbable polymer, when it is desired to produce membranes for medical applications. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In an embodiment for preparing membranes useful in medical applications the polymer is a biodegradable and/or bioabsorbable polymer which contains a monomer selected from the group consisting of a glycolid, lactide, dioxanone, caprolactone and trimethylene carbonate. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or heteropolymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran and polyamino acids. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable polymers include polylactides, poly-glycolides, polycaprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D, L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable polymers discussed above will have a molecular weight in the range of about 1,000 to about 1,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole. Blends of different molecular weight polymers are also contemplated. A small percentage of a low molar mass monomer can also be added to the higher molar mass polymer.

The methods and apparatus according to the invention are capable of producing membranes containing fibers having diameters in the range from about 10 up to about 1,000 nanometers, more preferably about 20 to about 500 nanometers.

It is also possible to produce membranes containing fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the membrane will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 80 wt %.

Membrane can also be produced containing fibers of different materials, e.g., different biodegradable and bioabsorbable polymers.

Optionally, additives, e.g., one or more medicinal agents, can be incorporated into the fibers produced in accordance with the invention. The additives can be mixed with the fiberizable material, e.g., polymer, prior to formation of the fibers.

The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology and the porosity of the non-woven membrane can be controlled to provide selectable performance criteria for the membranes being produced. The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the methods of the invention can provide a plurality of different layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity.

In such an embodiment, it is also contemplated that additives can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating additives into the fiber structure itself.

Membranes can be prepared for use in applications where the membrane contains a high percentage of very small diameter fibers or where relatively high surface area to structure is desired. As a consequence of preparing membranes using the present invention, the structure of the membrane can be tailored to contain a highly controlled amount of very small diameter fibrils or to exhibit an increased surface area over similar membranous structures prepared without the present invention. Moreover, the desired characteristics of the membranes can be maintained while producing the membranes at a rate higher than without the present invention.

Examples of membranes which exhibit the above described characteristics that can be produced according to the invention include medical devices or articles, such as drug delivery devices, adhesion-reducing barriers, scaffolding for guided tissue regeneration, anti-fibroblastic growth barriers, or nerve coaptation wraps, as well as non-medical devices or articles, such as separator membranes or current collectors useful in batteries or fuel cells. Further examples are described in co-pending, commonly owned patent application Ser. No. 09/859,007, entitled "Biodegradable and/or Bioabsorbable Fibrous Articles and Methods For Using The Articles For Medical Applications," filed on even date herewith.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane according to the invention was prepared as follows: a 30 wt % PLG copolymer/DMF solution was

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prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. 13.

Example 2

A membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (PAN) (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The geometry of the electrodes was designed in such a way so that the largest electric field strength could be achieved at the tip of the electrode under a given electric potential, which included a hemispherical tip with a radius of 0.125 inch and a central hole of 0.025 inch diameter. The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tip of the electrodes were 2 cm apart from each other. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorbable and biodegradable PAN membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image for the PAN membrane is shown in FIG. 14.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the

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solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. 15.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliter/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. 16 shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3 , as compared to the neat resin (PLA) density of 1.3 g/cm^3 .

Example 6

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 2 into a DMF solvent. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying solution feeding speed ranging from 20 $\mu\text{L/min}$ to 70 $\mu\text{L/min}$. An SEM of the resulting membrane is shown in FIG. 17.

Example 7

A biodegradable and bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and

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controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a biodegradable and bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 8

A biodegradable and bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a biodegradable and bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 9

A polyimide membrane was prepared according to the present invention as follows: First, a solution was prepared by slowly dissolving pyromellitic dianhydride (PMDA) and oxydianiline (ODA) in N,N-dimethylacetamide (DMAC) to provide a solution containing 10 wt % PMDA and 10 wt % ODA. The resulting solution was then reacted under condensation reaction conditions at a temperature of 50° C. for 30 minutes to provide a solution of poly(amic acid) pre-polymers. The yield was controlled to about 50% to avoid cross linking. The filtered and recovered poly(amic acid) solution contained about 10 wt % of solute. After the poly(amic acid) solution was completely homogenized at the room temperature, it was then loaded into a 5 ml syringe fitted with a gauge 20 needle and delivered through Teflon tubes to an electrode having a tiny hole with a diameter of 0.025". The pre-polymer solution was pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. A 25 kV positive high voltage was applied on the electrode in order to obtain the existence of a well-stabilized electrospinning jet. The distance from the tip of the electrode to the ground collecting plate was 15 cm. A step motor was utilized in order to control the movement of the ground

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collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 1 mm/sec continuously until a poly(amic acid) membrane having a relatively uniform thickness of 100 microns was achieved.

The poly(amic acid) membrane then subjected to a post-curing step to convert the membrane to a polyimide membrane. In the post-curing step, the poly(amic acid) membrane was imidized by thermal conversion by maintaining the membrane at about 250° C. under a vacuum for 120 minutes. The resulting membrane was yellowish with a silky tissue-paper like texture and had excellent environmental stability.

Example 10

Membranes useful as a separators or current collectors for a battery or fuel cell were prepared by subjecting a PAN membrane (prepared according to Example 2) and a polyimide membrane (prepared according to Example 9) each to a post-conditioning step in which a conductive layer was applied to the surface of each of the membranes. Since the membranes were not electrically conductive, they were plated with a thin layer of metal (e.g. copper) to induce conductivity using an electroless plating procedure. Electroless plating refers to the autocatalytic or chemical reduction of aqueous metal ions plated to a base substrate. This technique has been routinely used for coating of an object (such as a plastic part) as a pretreatment step. Unlike conventional electroplating, no electrical current is required for deposition. Components of the electroless bath typically include an aqueous solution of metal ions, catalyst, reducing agent(s), complex agent(s) and bath stabilizer(s). In electroless plating, the substrate being plated must be catalytic in nature (usually induced by surface pre-treatment) and can induce the autocatalytic reaction in the bath to continuously deposit the metal. The metal ions are reduced to metal by the action of the reducing agents.

The following electroless plating procedure was used to coat the membranes with copper: In a first step, each membrane was immersed in an acidic aqueous solution of stannous chloride (SnCl_2) (0.06 g SnCl_2 in 20 ml H_2O) kept at 45° C. for 30 minutes. In a second step, each of the recovered membranes from step 1 were immersed in a palladium chloride (PdCl_2) solution (having a concentration of 1 mg/ml of H_2O) at 70° C. for 60 minutes. An electroless copper bath was prepared by combining 15 g/liter of copper sulfide (metal salt), 40 g/liter of Rochelle salt (complexing agent), 6 ml/liter of 37% formaldehyde (reducing agent) and 0.01 g/liter of vanadium oxide (stabilizer). The pH level of the bath was kept at about 12 and the bath temperature at 70–75° C. Each membrane recovered from step 2 was immersed in the electroless copper bath for 30 minutes. The plating rate of this bath was about 1 to 5 $\mu\text{m/hr}$, with a target layer thickness of less than 100 microns. As the fiber surface to volume ratio is extraordinarily high and the fiber diameter is small, the plating process did not cover the entire contour of the membrane surface evenly. However, with plating of a large fraction of the membrane surface to the desired thickness, the resulting membrane exhibited sufficient electric conductivity for battery and fuel cell applications as separator membranes and current collectors. An SEM of the resulting copper plated PAN membrane is shown in FIG. 18.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing

from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A method for electrospinning a polymer fiber from a conducting fluid containing said polymer in the presence of a first electric field established between a conducting fluid introduction device and a ground source comprising:

modifying said first electric field with a second electric field to form a jet stream of said conducting fluid and forming a polymer fiber.

2. A method according to claim 1, wherein said conducting fluid introduction device is a spinneret.

3. A method according to claim 1, wherein said second electric field is established by imposing at least one field modifying electrode.

4. A method according to claim 3, wherein said field modifying electrode is a plate electrode positioned between said conducting fluid introduction device and said ground source.

5. A method according to claim 3, further comprising controlling the electrical potential on the conducting fluid introduction device by adjusting the electric charge on said field modifying electrode.

6. A method according to claim 3, further comprising imposing a plurality of electrical field modifying electrodes, to provide a controlled distribution of electrostatic potential along the direction of flow of said jet stream.

7. A method according to claim 1, further comprising feeding said conducting fluid to said conducting fluid introduction device at a controlled rate.

8. A method according to claim 7, wherein said rate is controlled by maintaining said conducting fluid at a constant pressure or constant flow rate.

9. A method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of an electric field established between a spinneret and a ground source comprising:

a) forming an electrospinning jet stream of said conducting fluid; and

b) electrically controlling the flow characteristics of said jet stream to provide a controlled pattern over a desired target area; and

c) forming a polymer fiber from said jet stream.

10. A method according to claim 9, wherein said flow characteristics of said jet stream are electrically controlled by at least one electrode.

11. A method according to claim 9, wherein said flow characteristics of said jet stream are electrically controlled by at least one pair of electrostatic quadrupole lenses.

12. A method according to claim 11, wherein said flow characteristics of said jet stream are electrically controlled by a plurality of pairs of electrostatic quadrupole lenses.

13. A method according to claim 12, wherein said flow characteristics of said jet stream are electrically controlled by using an alternating gradient technique.

14. A method according to claim 9, wherein said controlled pattern is provided by applying a waveform to the potential on at least one pair of electrostatic quadrupole lenses.

15. A method for forming a controlled-dimension and controlled-morphology membrane by electrospinning a plurality of polymer fibers from a conducting fluid containing said polymer in the presence of an electric field established between a solution introduction device and a ground source, said method comprising:

a) forming a plurality of electrospinning jet streams of said conducting fluid;

b) independently controlling the flow characteristics of at least one of said jet streams; and

c) forming a membrane.

16. A method according to claim 15, wherein said flow characteristics of at least one of said jet streams are controlled by at least one scanning electrode.

17. A method according to claim 15, wherein said flow characteristics of at least one or more of said jet streams are controlled by at least one pair of scanning electrodes.

18. A method according to claim 15, wherein said solution introduction device consists of a plurality of electrospinning spinnerets.

19. A method according to claim 18, wherein each spinneret produces an individual jet stream of said conducting fluid.

20. A method according to claim 19, wherein the flow characteristics of each individual jet stream is independently controlled.

21. A method according to claim 20, wherein each spinneret has at least one scanning electrode for electrically independently controlling the flow characteristics of each individual jet stream.

22. A method according to claim 21, wherein each spinneret has two pairs of scanning electrodes for electrically controlling the flow characteristics of each individual jet stream.

23. A method according to claim 18, wherein at least two spinnerets deliver different conducting fluids.

24. A method according to claim 23, wherein said different conducting fluids refers to different concentrations of polymer, different polymers, different polymer blends, different additives and/or different solvents.

25. An electrospinning apparatus for forming a membrane, comprising:

a conducting fluid introduction device for providing a quantity of conducting fluid containing a polymer, said conducting fluid introduction device comprising a plurality of electrospinning spinnerets for delivering said conducting fluid, said spinnerets being electrically charged at a first potential;

a ground member positioned adjacent said spinnerets and electrically charged at a second potential different from said first potential, thereby establishing an electric field between said spinnerets and said ground member;

a support member disposed between said spinnerets and said ground member and movable to receive conducting fluid from said spinnerets; and

means for controlling the flow characteristics of conducting fluid from at least one spinneret independently from the flow of conducting fluid from another spinneret.

26. An electrospinning apparatus according to claim 25, wherein said means for independently controlling the flow characteristics comprises at least one electrode disposed adjacent each spinneret, each electrode being charged at a potential different from and separate from said first potential.

27. An electrospinning apparatus according to claim 26, wherein each spinneret has two pairs of scanning electrodes for electrically separately directing the flow characteristics of conducting fluid from said spinneret.

28. An electrospinning apparatus according to claim 26, further comprising a probe associated with at least one spinneret, said probe being disposed between said electrode and said ground member, said probe being electrically charged at a potential different from said spinneret and said electrode.

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29. An electrospinning apparatus according to claim 25, wherein said means for independently controlling said flow characteristics comprises a means for individually electrically turning on and off a respective spinneret.

30. An electrospinning apparatus according to claim 29, wherein said means for individually electrically turning on and off a respective spinneret comprises at least one scanning electrode associated with each spinneret.

31. An electrospinning apparatus according to claim 25, wherein said means for independently controlling said flow characteristics comprises a means for applying an alternating gradient to said conducting fluid delivered from said spinnerets.

32. An electrospinning apparatus according to claim 31, wherein said means for applying said alternating gradient comprises a plurality of pairs of electrostatic quadropole lenses.

33. An electrospinning apparatus according to claim 25, wherein said apparatus further comprises a pump for supplying conducting fluid to said solution introduction device at a predetermined pressure.

34. An electrospinning apparatus according to claim 33, wherein said pump is adapted to control the supply rate of conductive fluid at a constant flow rate.

35. An electrospinning apparatus according to claim 33, wherein said pump is adapted to control the supply of conductive fluid at a constant pressure.

36. An electrospinning apparatus according to claim 25, wherein said apparatus comprises a pump system for supplying different conducting fluids to at least two individual spinnerets.

37. An electrospinning apparatus according to claim 25, wherein said solution introduction device comprises a slit-die defining said plurality of spinneret.

38. An electrospinning apparatus according to claim 37, wherein adjacent spinnerets are interconnected by slits.

39. An electrospinning apparatus according to claim 38, wherein said spinnerets are defining by openings in said slit-die and said slits interconnecting said spinnerets are of configurations smaller than said openings.

40. An electrospinning apparatus according to claim 37, further comprising a plurality of scanning electrodes disposed adjacent to each of said spinnerets.

41. An electrospinning apparatus according to claim 25, wherein said solution introduction device comprises a matrix defining said plurality of spinnerets, said spinnerets being disposed in said matrix in electrical isolation from each other.

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42. An electrospinning apparatus according to claim 41, wherein at least two individual spinnerets are electrically charged to a different potential.

43. An electrospinning apparatus according to claim 41, further comprising a plurality of individual electrodes wherein at least one individual electrode is disposed adjacent to each individual spinneret.

44. An electrospinning apparatus according to claim 43, wherein at least two of said individual electrodes are electrically charged to a different potential.

45. In an electrospinning apparatus for forming a membrane by electrospinning a plurality of polymer fibers from a conducting fluid which contains a polymer in the presence of an electric field between a conducting fluid introduction device and a ground source, an improved solution introduction device comprising:

a plurality of spinnerets, each for independently delivering a controlled quantity of conducting fluid at a constant pressure or constant flow rate, said spinnerets being charged at an electric potential and being disposed relative to each other to normally interfere with the electric field produced by adjacent spinnerets, each of said spinnerets having a tip at which conducting fluid exits configured to have an electrostatic field strength at each tip stronger than the liquid surface tension at each of said tips.

46. An improved solution introduction device according to claim 45, wherein each spinneret tip is configured by having a selected geometric profile, a selected spatial relationship relative to other spinneret tips or a combination of both.

47. An improved solution introduction device according to claim 46, further comprising an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets.

48. An improved solution introduction device according to claim 45, further comprising a means for at least partially shielding each spinneret tip from electric field interference from adjacent spinnerets.

49. An improved solution introduction device according to claim 48, wherein said means for at least partially shielding is a physical barrier disposed between adjacent spinnerets.

50. An improved solution introduction device according to claim 49, wherein said physical barrier has a conical shape.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,011 B2
DATED : March 30, 2004
INVENTOR(S) : Chu et al.

Page 1 of 1

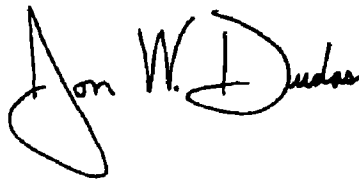
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,

Line 4, insert: -- "This invention was made with government support under the following Grant Nos. DAAG559710022 awarded by the U.S. Army Research Office and DEFG0286ER45237.015 awarded by the U.S. Department of Energy. The Government has certain rights in the invention." --

Signed and Sealed this

Sixth Day of July, 2004

A handwritten signature in black ink, appearing to read "Jon W. Dudas". The signature is written in a cursive, stylized font. Below the signature is a horizontal line.

JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,011 B2
DATED : March 30, 2004
INVENTOR(S) : Chu et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 9,

Line 32, now reads "spirmeret tip as discussed above.", and should read -- spinneret tip as discussed above. --;

Column 20,

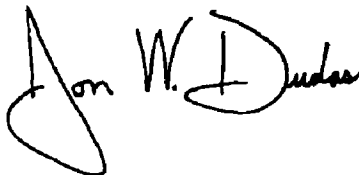
Line 1, now reads "a plurality of electrospinniflg", and should read -- a plurality of electrospinning --;

Column 21,

Line 36, now reads "adjacent spinnemets are", and should read -- adjacent spinnerets are --.

Signed and Sealed this

Twelfth Day of October, 2004

A handwritten signature in black ink, reading "Jon W. Dudas". The signature is stylized, with a large, looped initial "J" and a cursive "Dudas".

JON W. DUDAS
Director of the United States Patent and Trademark Office



US007172765B2

(12) **United States Patent**
Chu et al.

(10) **Patent No.:** **US 7,172,765 B2**
(45) **Date of Patent:** **Feb. 6, 2007**

(54) **BIODEGRADABLE AND/OR
BIOABSORBABLE FIBROUS ARTICLES AND
METHODS FOR USING THE ARTICLES FOR
MEDICAL APPLICATIONS**

4,323,525 A	4/1982	Bornat
4,345,414 A	8/1982	Bornat et al.
4,468,922 A	9/1984	McCrary et al.
4,689,186 A	8/1987	Bornat
4,810,180 A	3/1989	Isner
4,840,626 A	6/1989	Linsky et al.
4,878,908 A	11/1989	Martin et al.

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(Continued)

FOREIGN PATENT DOCUMENTS

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 411 days.

WO WO98/03267 1/1998

(21) Appl. No.: **10/719,290**

(Continued)

(22) Filed: **Nov. 21, 2003**

OTHER PUBLICATIONS

(65) **Prior Publication Data**

US 2004/0076661 A1 Apr. 22, 2004

Bezwaada et al., "Poly(p-Dioxanone) and Its Copolymers," *Hand-
book of Biodegradable Polymers*, # 29-61 (1997).

(Continued)

Related U.S. Application Data

Primary Examiner—Carlos A. Azpuru

(62) Division of application No. 10/375,329, filed on Feb.
27, 2003, now Pat. No. 6,689,374, and a division of
application No. 09/859,007, filed on May 16, 2001,
now Pat. No. 6,685,956.

(74) Attorney, Agent, or Firm—Hoffmann & Baron, LLP

(57)

ABSTRACT

(51) **Int. Cl.**

A61F 2/02 (2006.01)

(52) **U.S. Cl.** **424/423; 424/424; 424/425;
424/426**

(58) **Field of Classification Search** **424/423,
424/424, 425, 426**
See application file for complete search history.

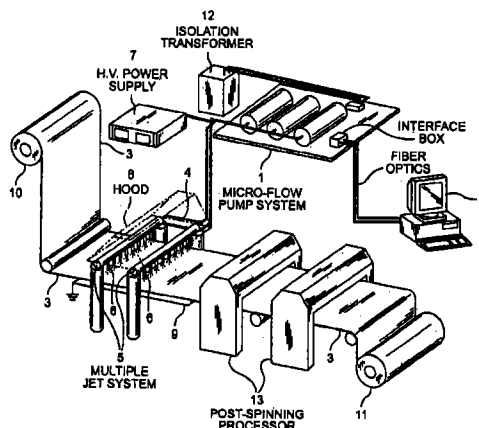
(56) **References Cited**

U.S. PATENT DOCUMENTS

3,975,565 A	8/1976	Kendall
4,043,331 A	8/1977	Martin et al.

Biodegradable and/or bioabsorbable fibrous articles and
methods for using the articles in medical applications are
disclosed. The biodegradable and/or bioabsorbable fibrous
articles, which are formed by electrospinning fibers of bio-
degradable and/or bioabsorbable fiberizable material, com-
prise a composite (or asymmetric composite) of different
biodegradable and/or bioabsorbable fibers. Articles having
specific medical uses include an adhesion-reducing barrier
and a controlled delivery system. The methods include
methods for reducing surgical adhesions, controlled delivery
of a medicinal agent and providing controlled tissue healing.

60 Claims, 14 Drawing Sheets



US 7,172,765 B2

Page 2

U.S. PATENT DOCUMENTS

4,911,867 A 3/1990 Burlet et al.
5,066,755 A 11/1991 Lemstra
5,296,172 A 3/1994 Davis et al.
5,480,436 A 1/1996 Bakker et al.
5,508,036 A 4/1996 Bakker et al.
5,569,528 A 10/1996 Van der Loo et al.
5,714,159 A 2/1998 Shalaby
5,783,111 A 7/1998 Ikkala et al.
5,795,584 A 8/1998 Totakura et al.
6,010,692 A 1/2000 Goldberg et al.
6,013,371 A 1/2000 Hager et al.
6,037,331 A 3/2000 Shalaby et al.
6,056,970 A 5/2000 Greenawalt et al.
6,060,582 A 5/2000 Hubbell et al.
6,090,910 A 7/2000 Shinoda et al.

6,106,913 A 8/2000 Scardino et al.
6,218,441 B1 4/2001 Meluch et al.
6,685,956 B2 * 2/2004 Chu et al. 424/423
6,689,374 B2 * 2/2004 Chu et al. 424/423

FOREIGN PATENT DOCUMENTS

WO WO01/26610 A1 4/2001
WO WO01/27365 A1 4/2001

OTHER PUBLICATIONS

Dzenis et al., "Polymer Hybrid Nano/Micro Composites," *Proceedings of the American Society for Composites—Ninth Technical Conference*, pp. 657-665 (1994).

* cited by examiner

FIG. 1

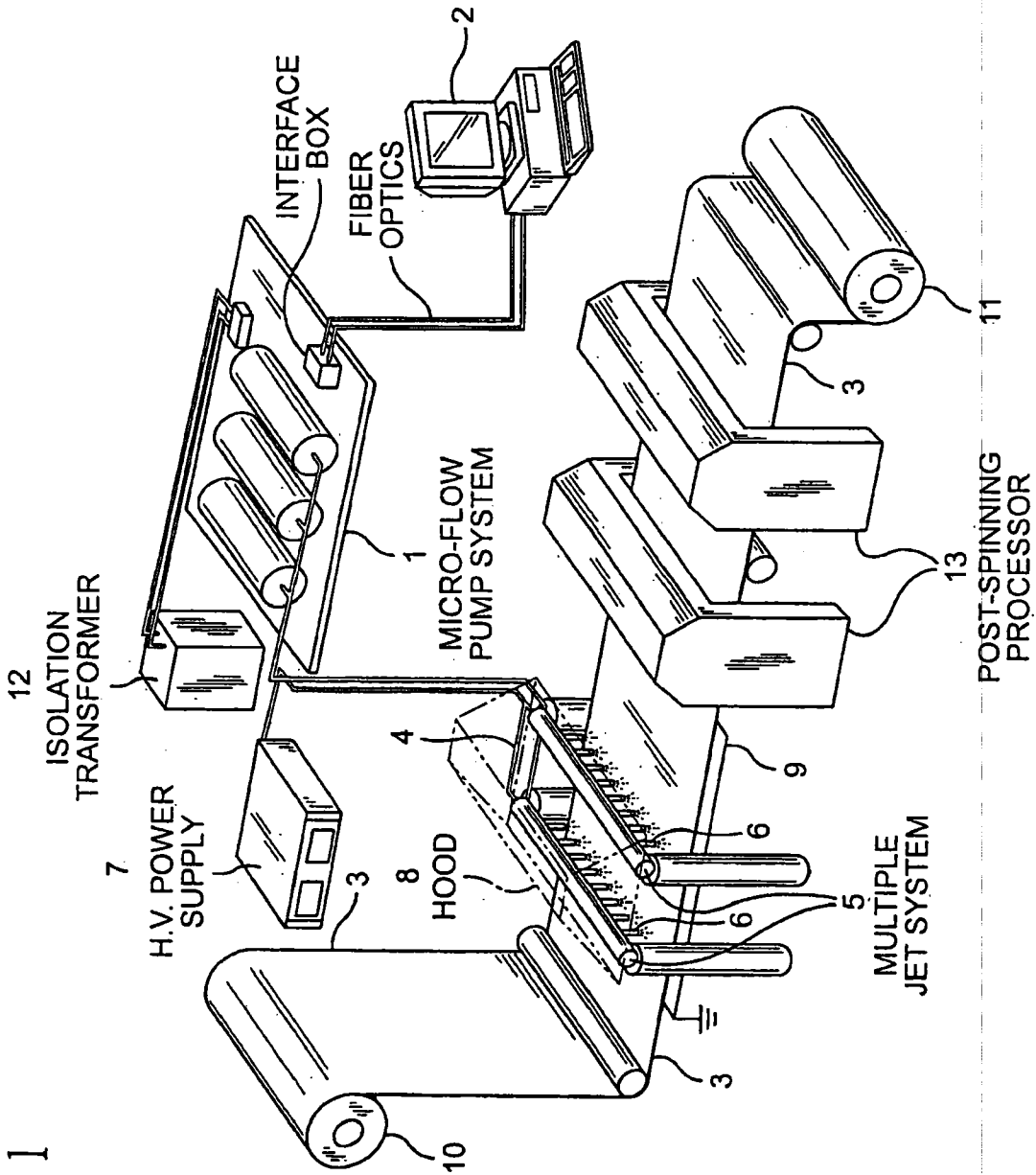


FIG. 2 (a)

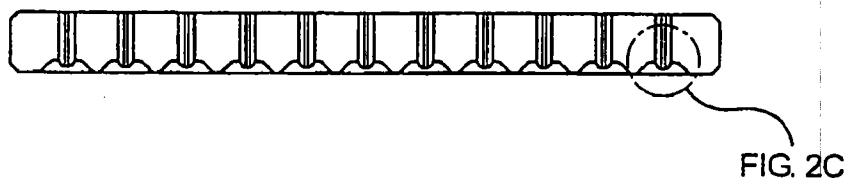


FIG. 2 (b)

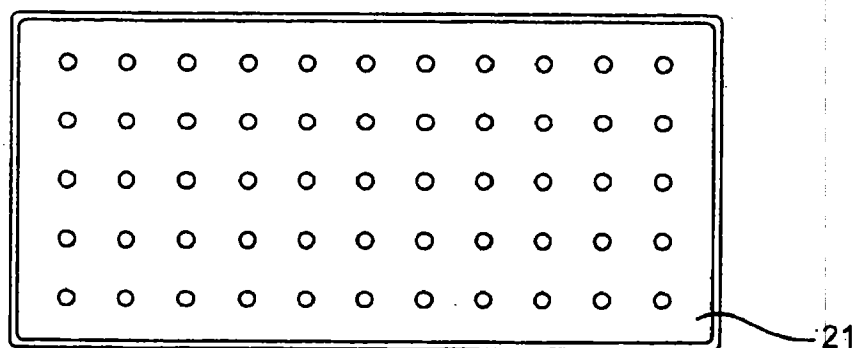


FIG. 2 (c)

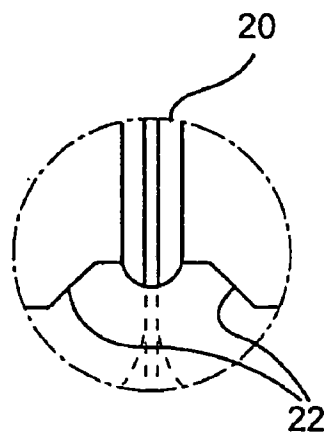


FIG. 3 (a)

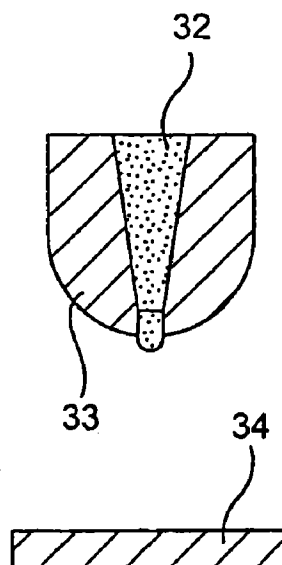


FIG. 3 (b)

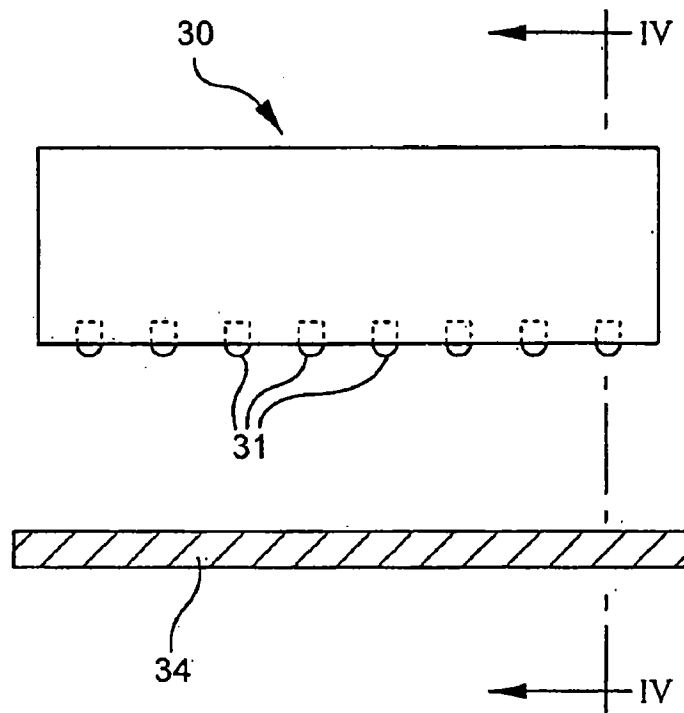


FIG. 3 (c)

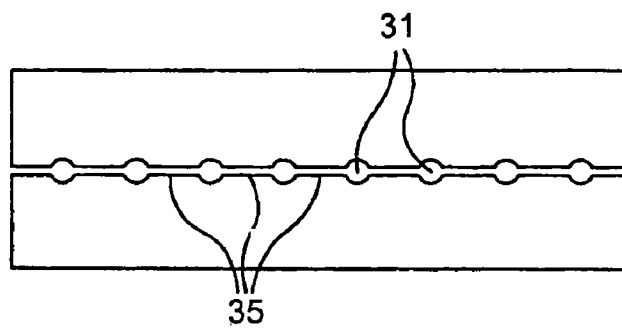


FIG. 4 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

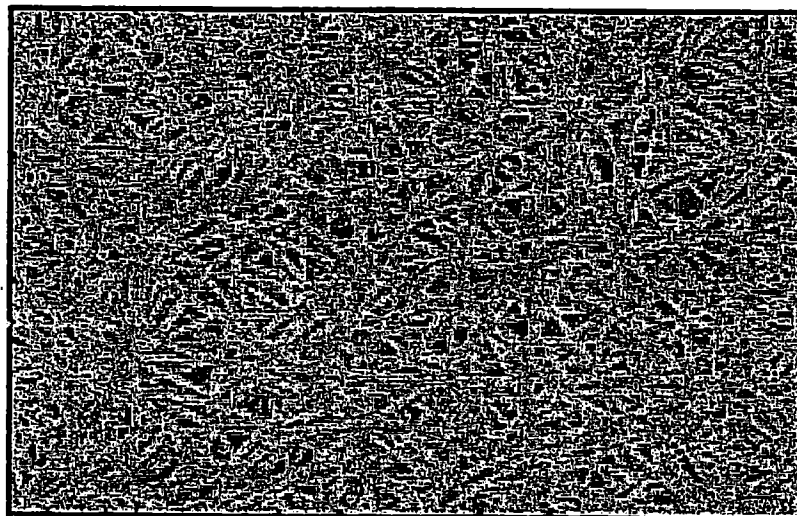
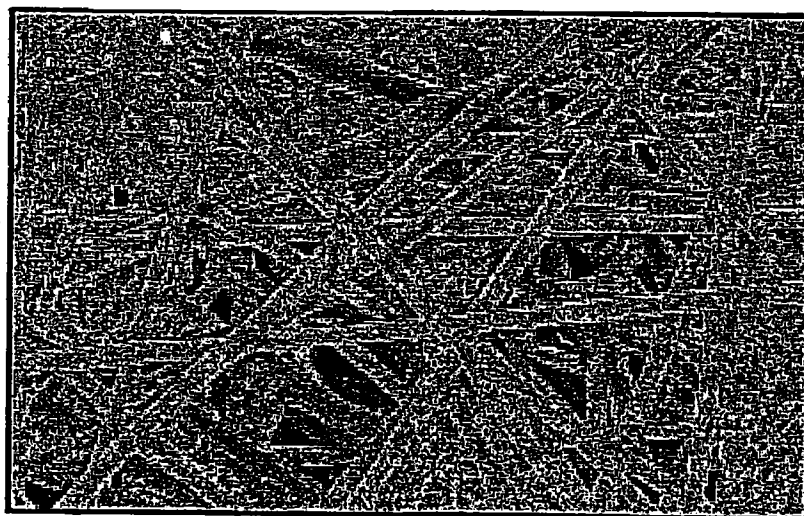


FIG. 5 SPUN MEMBRANE WITHOUT SALT



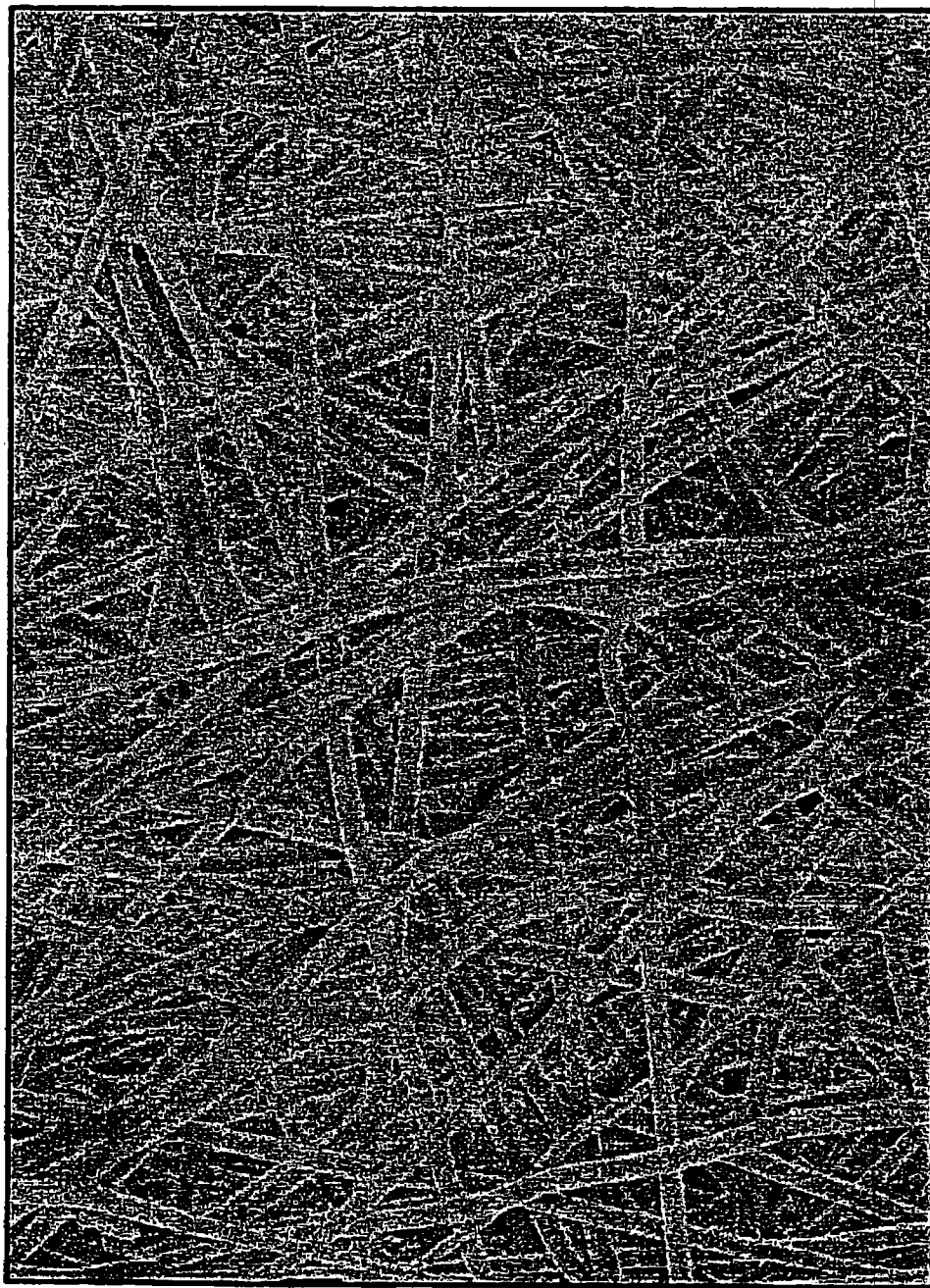


FIG. 6

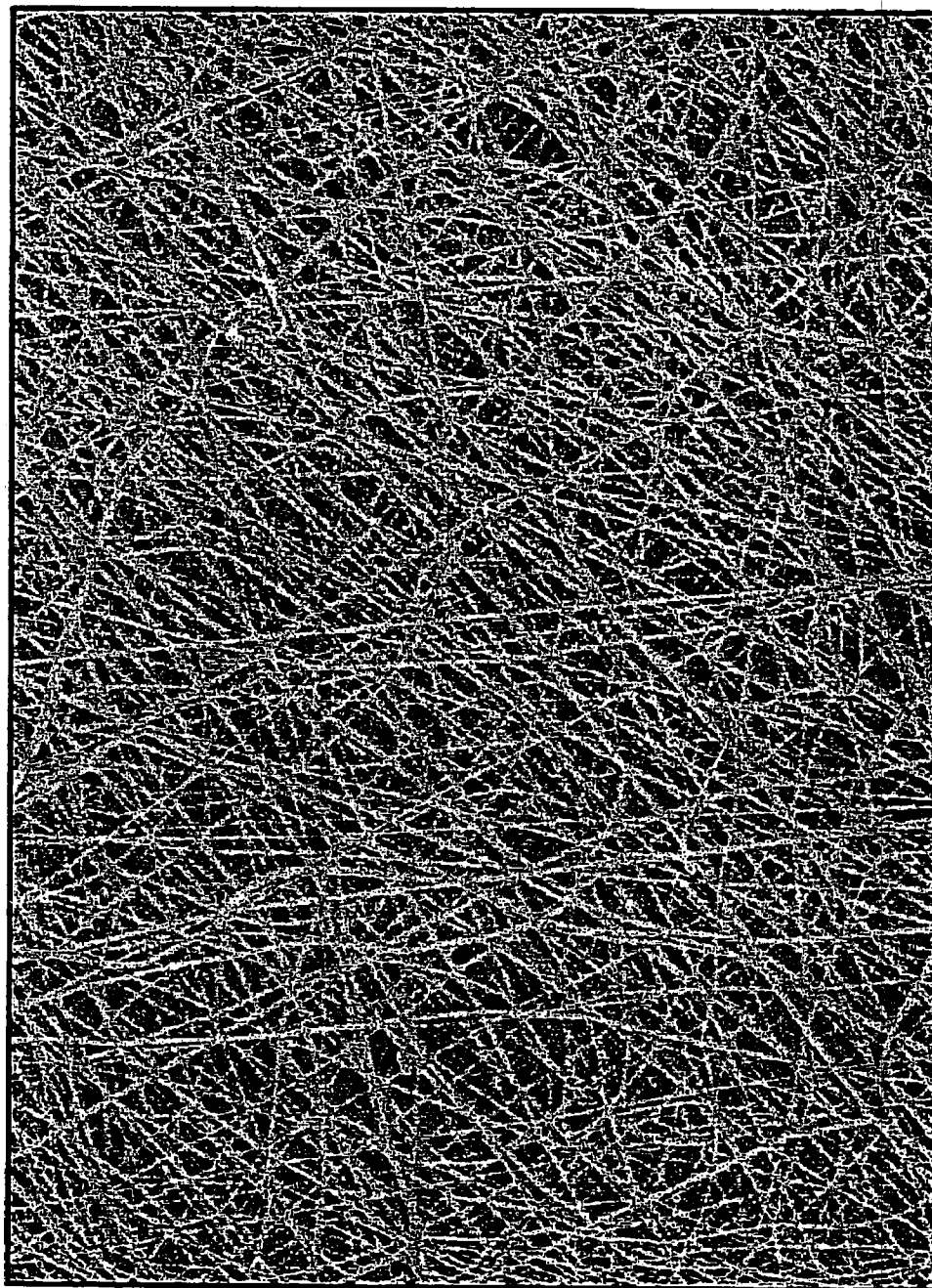


FIG. 7

FIG. 8 IN VITRO DRUG RELEASE PROFILE

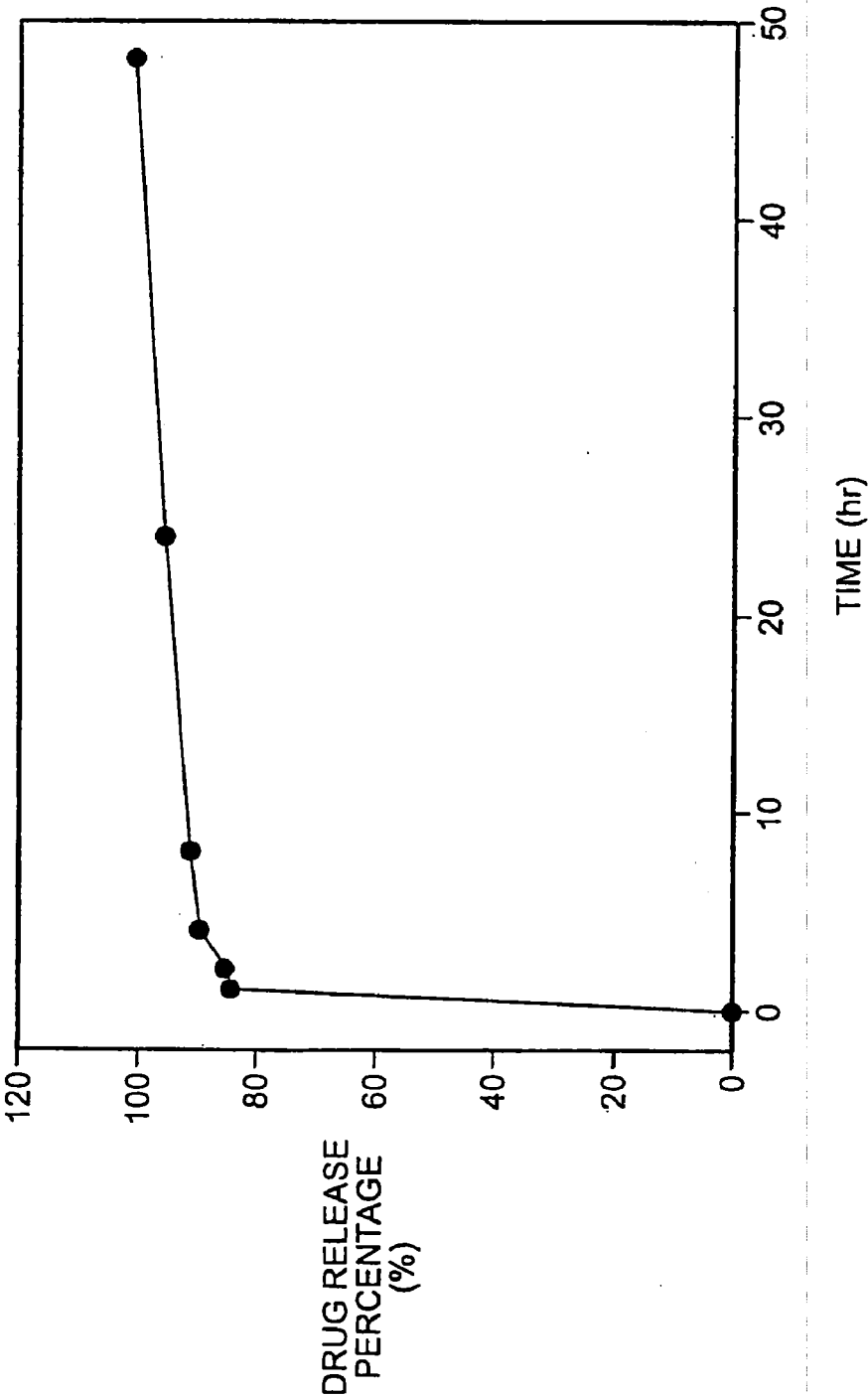
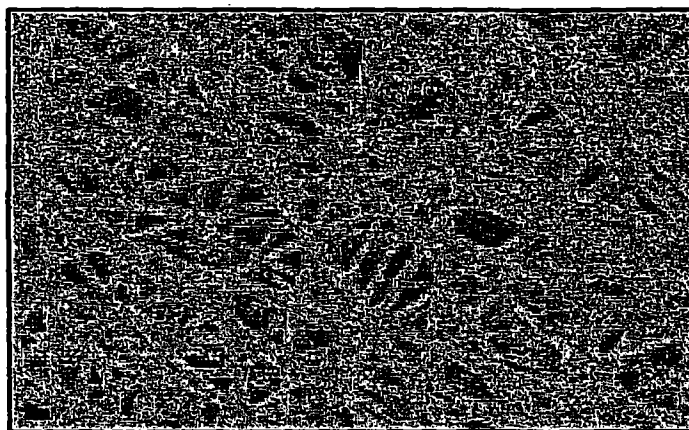
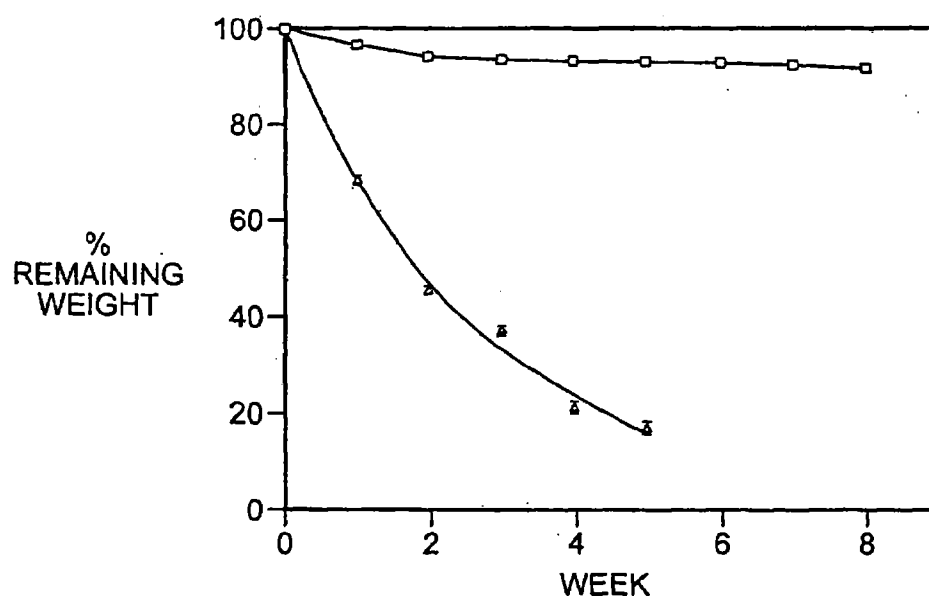


FIG. 9 SEM IMAGE OF ELECTROSPUN PLA MEMBRANEFIG. 10 BIODEGRADATION RATE OF ELECTROSPUN MEMBRANE

▲ AMORPHOUS PGA FILM

□ P(DL)LA ELECTROSPUN FILM

FIG. 11 DUEL THICKNESS PLA MEMBRANE



FIG. 12 MEMBRANE AFTER 1 WEEK OF DEGRADATION

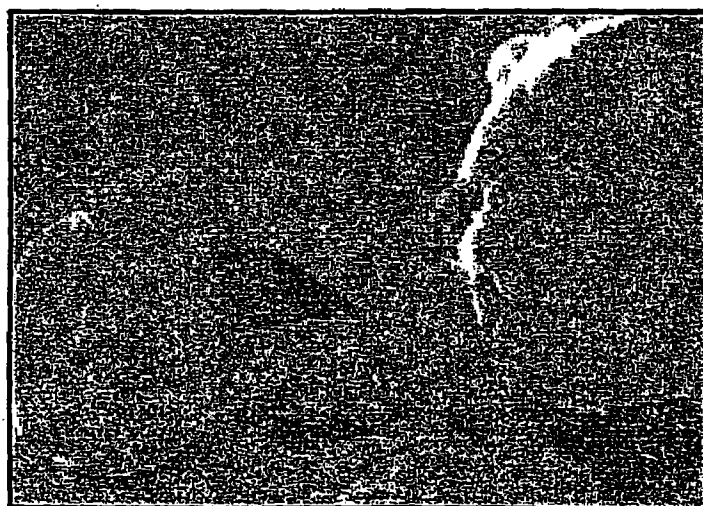


FIG. 13 INCIDENCE OF ADHESION

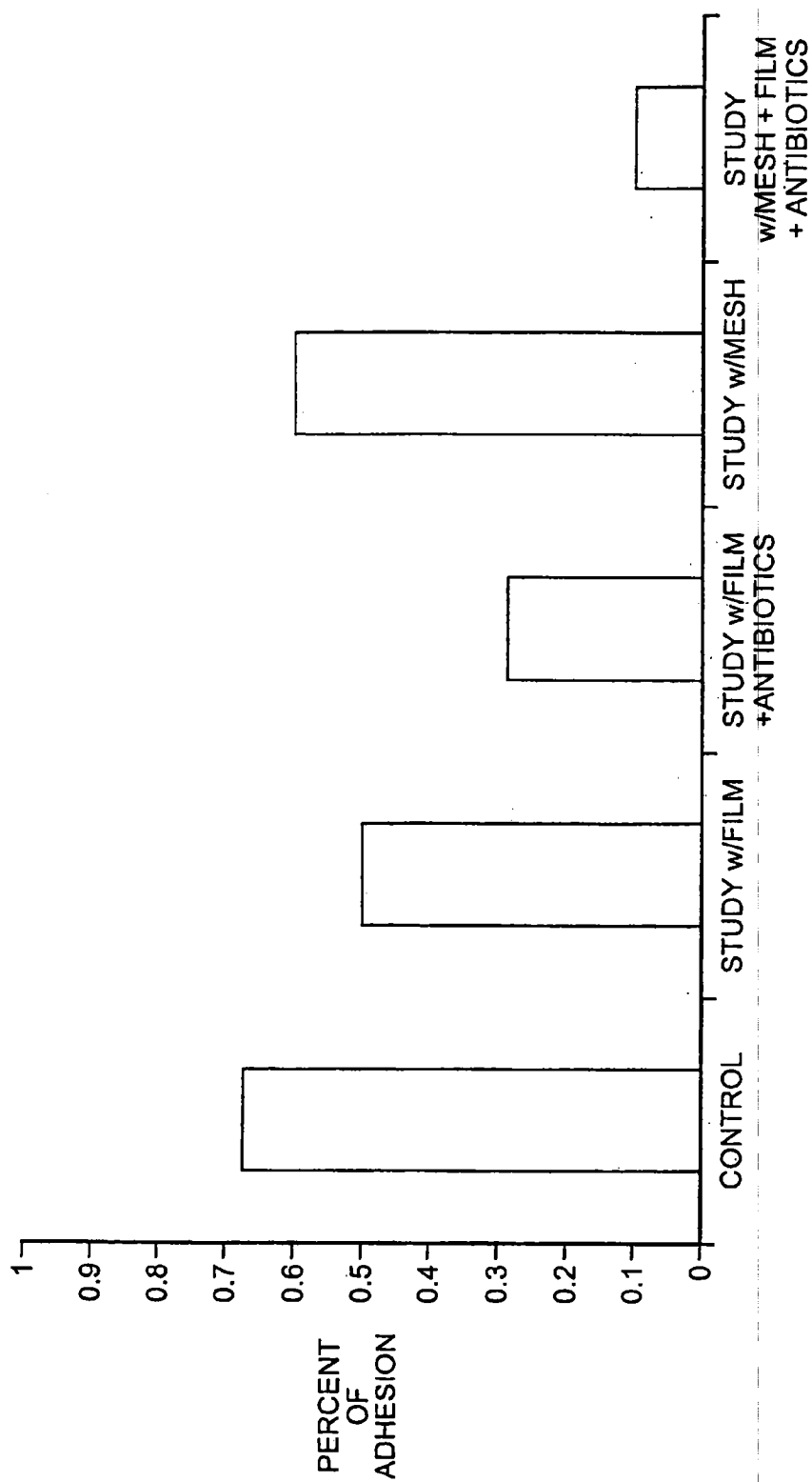


FIG. 14 CECAL ADHESION TENSION (N)

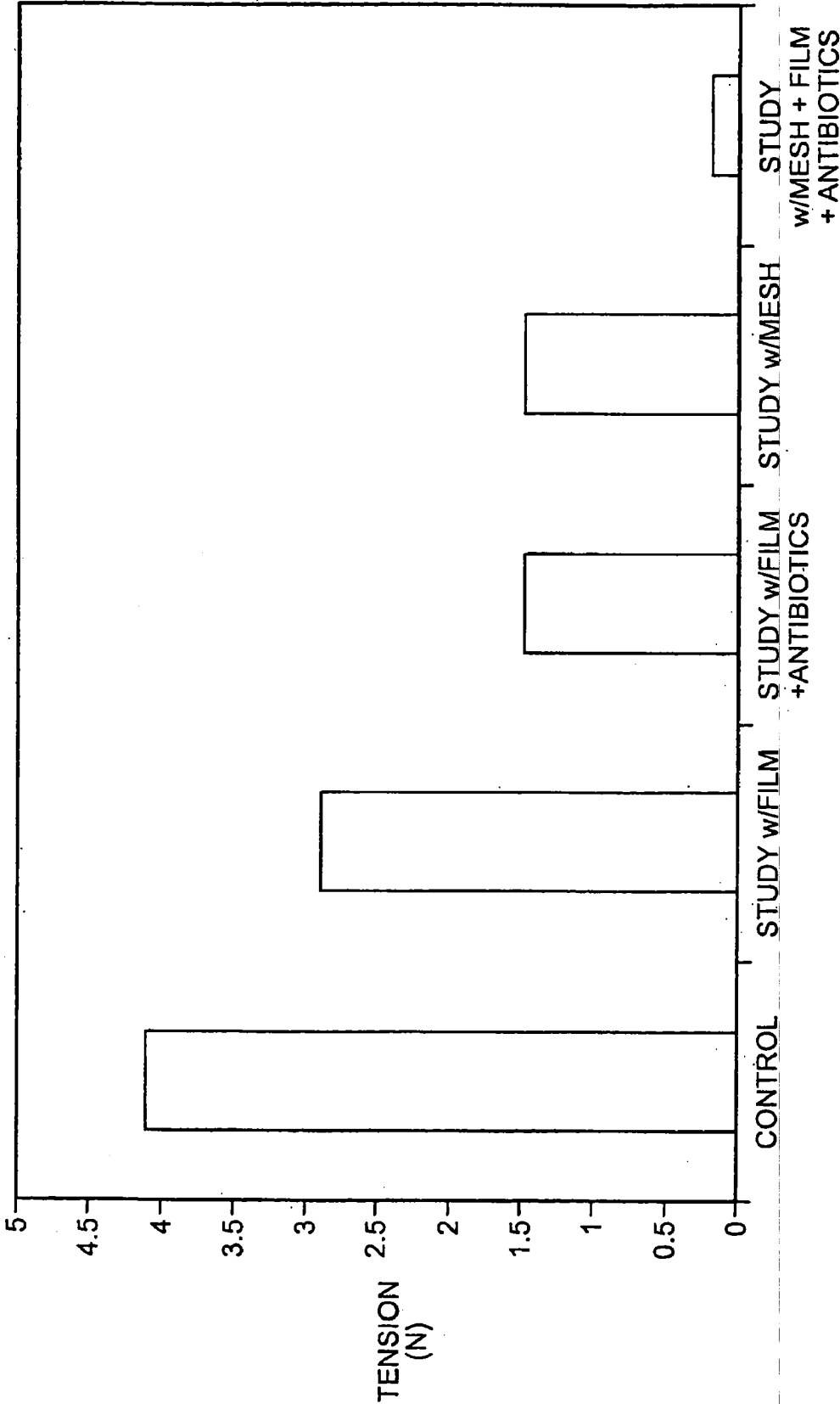


FIG. 15 ANTIBACTERIAL TEST RESULTS OF PLA MEMBRANE

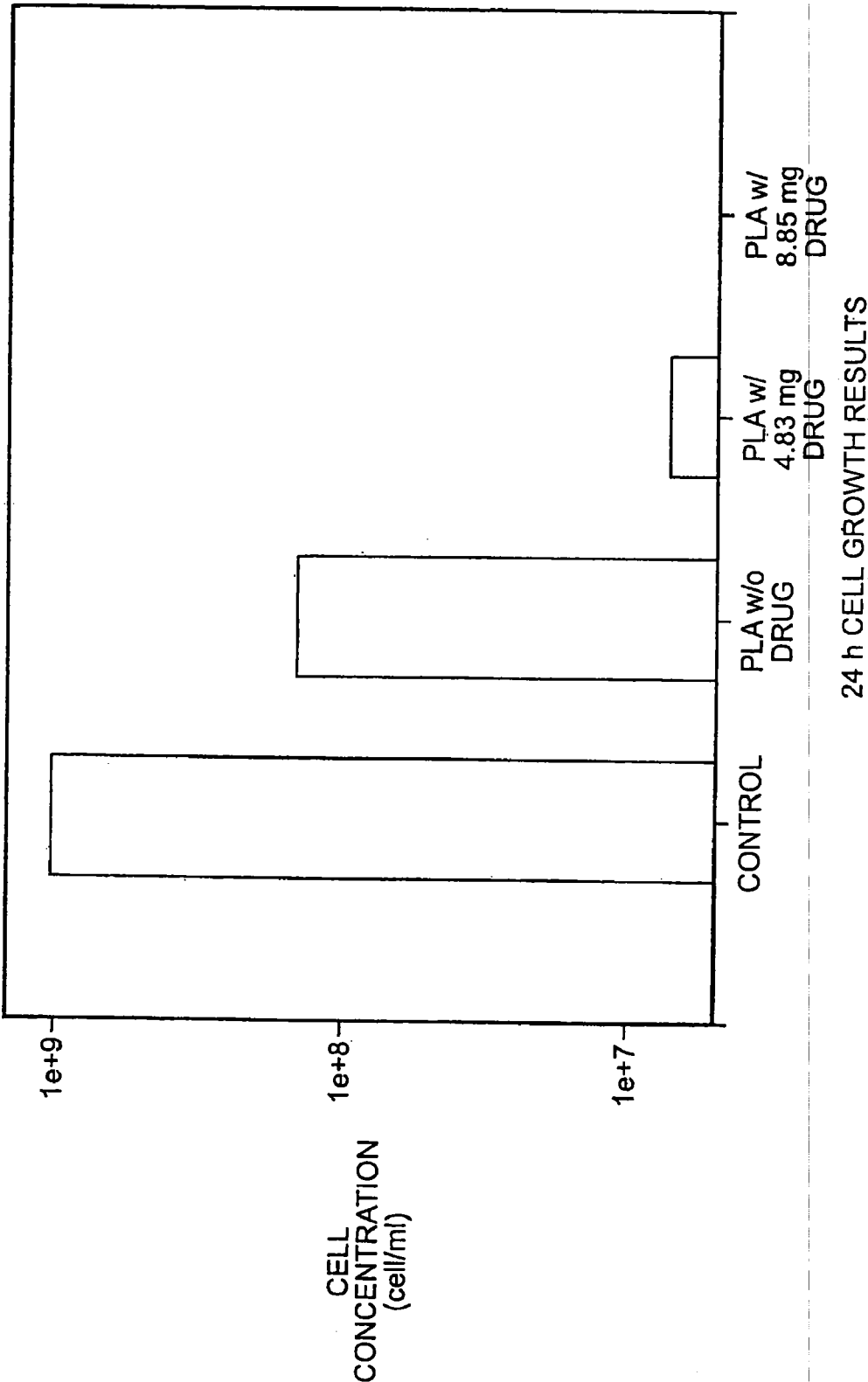


FIG. 16 SEM IMAGE OF AS-SPUN MEMBRANE

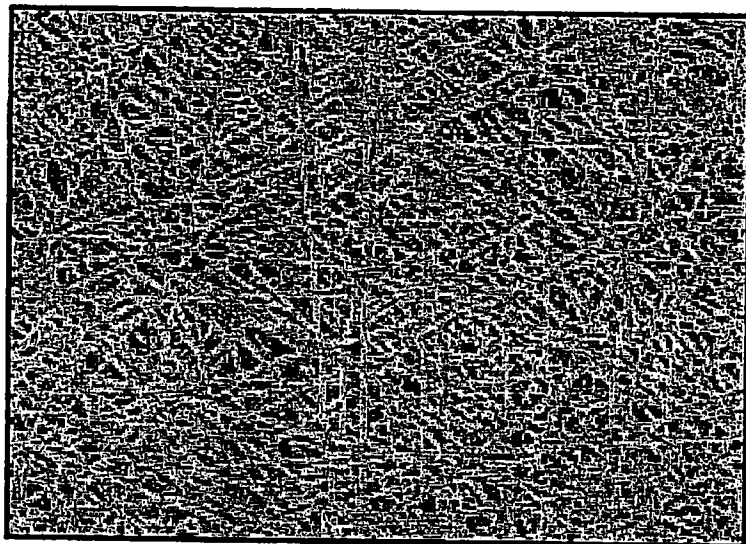
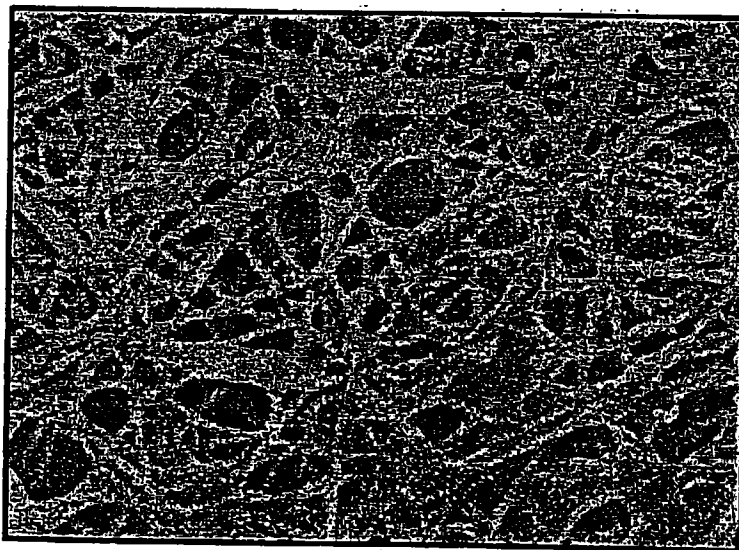


FIG. 17 IN-VIVO DEGRADATION AFTER A WEEK



**BIODEGRADABLE AND/OR
BIOABSORBABLE FIBROUS ARTICLES AND
METHODS FOR USING THE ARTICLES FOR
MEDICAL APPLICATIONS**

This application is a divisional of application Ser. No. 10/375,329, filed on Feb. 27, 2003 now U.S. Pat. No. 6,689,374 Ser. No. 09/859,007 filed on May 16, 2001.

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fibrous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the

formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokine) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-

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fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminoglycan can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning

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fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

In one embodiment, the above described fibrous articles are in the form of a membrane.

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The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the composite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegradation rate with utility in a controlled delivery system.

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Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic of an electrospinning system.

FIG. 2 is a schematic of an array of spinnerets for an electrospinning process.

FIG. 3(a) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. 3(b) is a cross-sectional view of the spinneret system of FIG. 3(a) as seen along viewing lines IV—IV thereof.

FIG. 3(c) is a bottom view of the multiple spinneret system of FIG. 3(a).

FIG. 4 is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4 .

FIG. 5 is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. 6 is an SEM of a membrane described in Example 1.

FIG. 7 is an SEM of a membrane described in Example 4.

FIG. 8 is a graph of the results of the drug release test described in Example 4.

FIG. 9 is an SEM of a PLA membrane described in Example 5.

FIG. 10 is a graph of the results of the biodegradation tests described in Example 6.

FIG. 11 is an SEM of the PLA membrane described in Example 7.

FIG. 12 is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. 13 is a graph of the results of the adhesion experiment described in Example 8.

FIG. 14 is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. 15 is a graph of the results of the antibacterial test described in Example 9.

FIG. 16 is an SEM of the as spun membrane described in Example 10.

FIG. 17 is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers*, in *Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29-61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA

spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginate acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include poly(lactides), poly-glycolides, polycaprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000

nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorbable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, anti-muscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that

follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorbable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between muscle tissue and bone; barriers between the esophagus and mediastinum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal

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hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioabsorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

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All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsorbable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6 . If the extrudate (conducting fluid) from each spinneret has a rate of about 10 $\mu\text{l}/\text{min}$, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

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The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4 , K_2HPO_4 , KIO_3 , KCl, MgSO_4 , MgCl_2 , NaHCO_3 , CaCl_2 , or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. 1. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. 1, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system 1. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4 . Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system 1 is linked to a computer 2 which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane 3 and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system 1 feeds the conducting fluid to a multiple jet system 4 that contains manifolds 5 having a bank of spinnerets 6. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply 7. A hood 8 is positioned over the multiple jet system 4 to remove the solvent at a controlled evaporation rate.

A ground plate 9 is positioned below the multiple jet system 4 such that an electric field is created between the charged spinnerets 6 and the ground plate 9. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate 9, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support 3 is positioned between the charged spinnerets 6 and the ground plate 9 to collect the fibers which are formed from the spinnerets and to form an interconnected web of the fibers. The support 3 moves in the direction from the unwind roll 10 to the rewind roll 11.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer 12.

The post-spinning processors 13 have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thick-

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ness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed 05/16/2001, now U.S. No. 6,703,011.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magnetohydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2-3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be

removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another method for producing membranes according to the present invention, reference will be made to FIG. 2. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets 20. The array of electrospinning spinnerets are assembled in a matrix 21 that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes 22. The spinneret 20 and the scanning electrodes 22 are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret 20 can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret 20 can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. 3(a)-3(c). In this apparatus, a multiple jet system 30 comprises an array of electrospinning spinnerets 31, each spinneret 31 being defined by a slit 32 formed in a slit-die 33 that is coupled to high voltage to serve as an electrode disposed above the ground plate 34. As shown in detail in FIG. 3(c), the spinnerets 31 are each interconnected by selectively narrow slits 35, such that each spinneret 31 is interconnected to a neighboring spinneret 31 by a slit 35. The conducting fluid will not flow through the slits 35, but will flow through each of the spinnerets 31 in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with con-

trolled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate Through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. 4) than the one with no salt added (FIG. 5). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4 , KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55-0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The dis-

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tance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. 6.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorbable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then

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very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. 7.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 nm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. 8.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. 9 shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3 , as compared to the neat resin (PLA) density of 1.3 g/cm^3 .

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. 10. A review of FIG. 10 reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 $\mu\text{L}/\text{min}$ to 70 $\mu\text{L}/\text{min}$. An SEM of the resulting membrane is shown in FIG. 11.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared (FIG. 12). A comparison of FIGS. 11 and 12 reveals that this morphology results in a rapid weight loss in the first week.

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Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ -radiation doses from 5.15–25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylazine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A 1×1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned are (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibodies (see FIG. 13). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. 14). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while 10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh

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placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1×1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10). All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesion strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0×7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. 15, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. 15 reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conducted using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug ration of 9:1. A 20 kV positive voltage was applied to the

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electrode. An SEM of the initial as spun membrane (FIG. 16) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. 17.

A comparison of FIGS. 16 and 17 reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorbable membrane having a relatively uniform thickness of 100 microns was achieved.

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Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material comprising a composite of different biodegradable and/or bioabsorbable fibers.
2. A fibrous article according to claim 1, wherein said composite of different fibers is defined by fibers of different diameters.
3. A fibrous article according to claim 2, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.
4. A fibrous article according to claim 3, wherein said fibrous article comprises at least about 20 weight percent of submicron diameter fibers.
5. A fibrous article according to claim 4, wherein said fibrous article comprises at least about 50 weight percent of submicron diameter fibers.
6. A fibrous article according to claim 1, wherein said composite of different fibers is defined by fibers of different biodegradable and/or bioabsorbable materials.
7. A fibrous article according to claim 1, wherein said composite of different fibers is defined by fibers of different diameters and different biodegradable and/or bioabsorbable materials.
8. A fibrous article according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.
9. A fibrous article according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.
10. A fibrous article according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.
11. A fibrous article according to claim 10, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).
12. A fibrous article according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.
13. A fibrous article according to claim 1, wherein said fibers have diameters in the range from about 10 up to about 1,000 nanometers.
14. A fibrous article according to claim 13, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.
15. A fibrous article according to claim 1, further comprising small blobs of biodegradable and/or bioabsorbable material.
16. A fibrous article according to claim 1, further comprising at least one medicinal agent.
17. A fibrous article according to claim 16, wherein said medicinal agent is contained within said fibers.

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18. A fibrous article according to claim 17, further comprising fibers with different concentrations of said medicinal agent.

19. A fibrous article according to claim 17, further comprising fibers with different medicinal agents.

20. A fibrous article according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite of different biodegradable and/or bioabsorbable fibers.

21. A fibrous article according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

22. A fibrous article according to claim 1, wherein said fibrous article has a controlled degradation rate.

23. A fibrous article according to claim 1, wherein said fibrous article is a membrane.

24. A fibrous article according to claim 23, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

25. A fibrous article according to claim 24, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

26. A fibrous article according to claim 1, wherein said composite is an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

27. A fibrous article according to claim 26, wherein different fibers refers to fibers of different diameters.

28. A fibrous article according to claim 27, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.

29. A fibrous article according to claim 28, wherein said fibrous article comprises at least about 20 weight percent of submicron diameter fibers.

30. A fibrous article according to claim 29, wherein said fibrous article comprises at least about 50 weight percent of submicron diameter fibers.

31. A fibrous article according to claim 26, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

32. A fibrous article according to claim 26, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

33. A fibrous article according to claim 26, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

34. A fibrous article according to claim 33, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

35. A fibrous article according to claim 33, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

36. A fibrous article according to claim 35, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

37. A fibrous article according to claim 26, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

38. A fibrous article membrane according to claim 26, wherein said fibers have diameters in the range from about 10 up to about 1,000 nanometers.

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39. A fibrous article according to claim 38, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

40. A fibrous article according to claim 26, further comprising small blobs of biodegradable and/or bioabsorbable material.

41. A fibrous article according to claim 26, further comprising at least one medicinal agent.

42. A fibrous article according to claim 41, wherein said medicinal agent is contained within said fibers.

43. A fibrous article according to claim 42, further comprising fibers with different concentrations of said medicinal agent.

44. A fibrous article according to claim 42, further comprising fibers with different medicinal agents.

45. A fibrous article according to claim 26, wherein said fibrous article has a controlled degradation rate.

46. A fibrous article according to claim 26, wherein said fibrous article is a membrane.

47. A fibrous article according to claim 46, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

48. A fibrous article according to claim 47, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

49. A fibrous article formed by electrospinning different fibers of different materials, comprising a composite of different fibers which comprises fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

50. A fibrous article according to claim 49, wherein said different fibers comprise submicron diameter fibers.

51. A fibrous article according to claim 49, wherein said composite is an asymmetric composite of said different fibers.

52. A method for reducing surgical adhesions which comprises positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue, said barrier comprising a biodegradable and/or bioabsorbable membrane, wherein said membrane comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers; a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

53. A method according to claim 52, wherein different fibers refers to fibers of different diameters.

54. A method according to claim 52, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

55. A method according to claim 52, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

56. A method for providing controlled tissue healing which comprises implanting at a target site in an animal, a system for controlled tissue healing, said system comprising a biodegradable and/or bioabsorbable fibrous article, wherein said fibrous article comprises a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

57. A method according to claim 56, wherein said fibrous article is selected from the group consisting of a scaffold for guided tissue regeneration, a protective covering for redirecting healing, a protective covering for weakened tissue and an anti-fibroblastic growth barrier.

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58. A method according to claim **56**, wherein different fibers refers to fibers of different diameters.

59. A method according to claim **56**, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

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60. A method according to claim **56**, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,172,765 B2
APPLICATION NO. : 10/719290
DATED : February 6, 2007
INVENTOR(S) : Chu et al.

Page 1 of 1

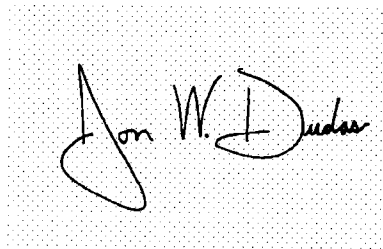
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, Line 5, after the title, insert:

--This invention was made with government support under Grant Nos. DMR 9984102 and DMR 9732653 awarded by the National Science Foundation. The Government has certain rights in the invention.--

Signed and Sealed this

Twenty-fourth Day of July, 2007

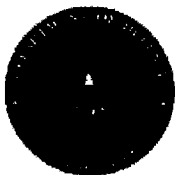
A handwritten signature in black ink, reading "Jon W. Dudas", is placed over a rectangular area with a light gray dot grid background.

JON W. DUDAS

Director of the United States Patent and Trademark Office

EXHIBIT C

Subj: **Army 02.2 Phase I SBIR Solicitation**
Date: 11/11/2002 3:51:14 PM Eastern Standard Time
From: MeagherK-Contractor@hqamc-exchg.army.mil
To: dfangstar@aol.com
Sent from the Internet ([Details](#))



REPLY TO
THE ATTENTION OF

DEPARTMENT OF THE ARMY
UNITED STATES ARMY RESEARCH LABORATORY
UNITED STATES ARMY RESEARCH OFFICE - WASHINGTON
5001 EISENHOWER AVENUE (ROOM 8N31)
ALEXANDRIA, VIRGINIA 22333-0001

November 11, 2002

Dr. Dufei Fang
Stonybrook Technology and Applied Research, Inc.
P.O. Box 1336
Stony Brook, NY 11790

Subject: Army 02.2 Phase I SBIR Solicitation
Topic #: A02-193
Control #: A022-2903

Dear Dr. Fang:

This letter informs you that your proposal entitled "Novel Clothing Nonwoven Liner Material - Nanofibers in Melt Blown Media" submitted to the Army Small Business Innovation Research (SBIR) Program, has been competitively selected for negotiation and possible contract award. The contract award to fund your proposed work is contingent upon successful negotiations through the assigned Contracting Officer and availability of funds. Consequently, please be advised that the Government is not responsible for any funds expended by offerors prior to award of signed contracts.

You will soon be contacted by a designated procurement official within the cognizant Army Laboratory or Center to initiate the contract award process.

Sincerely,

Janice M. Baker
MAJ, USA
Army SBIR Program Manager